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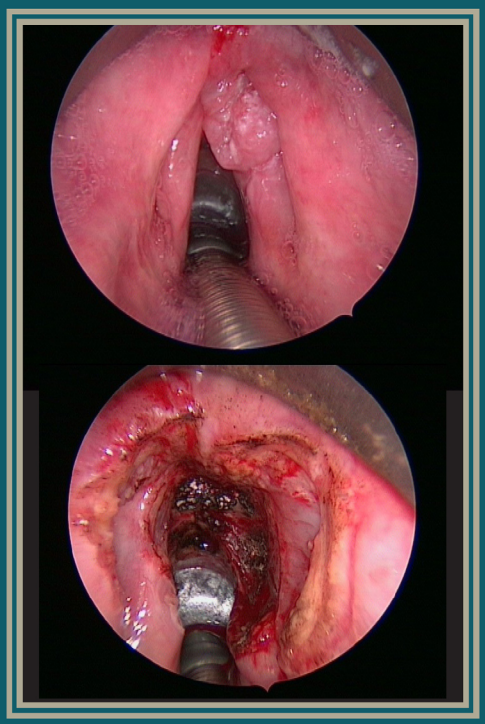

VOLUME 3

Head & Neck Surgery Plastic Surgery

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Raymond W Clarke

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Otorhinolaryngology Head and Neck Surgery

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VOLUME 3

Head and Neck Surgery, Plastic Surgery

Scott-Brown's Otorhinolaryngology Head and Neck Surgery

EIGHTH EDITION

VOLUME 3

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Foreword

The eighth edition of *Scott-Brown* signals the beginning of a new and exciting era for ear, nose and throat surgeons, and also the end of 10 years of very hard work undertaken by John Watkinson and Ray Clarke, the Editors-in-Chief, their team of subeditors and, not least, the publishers. Whatever subspeciality the current generation of trainees decides to follow, they will all have to read and refer to *Scott-Brown* in order to complete their education and gain accreditation. It will be a constant companion and guide throughout their professional lives.

When asked to write the foreword for this edition, I was immediately reminded that I had read John Ballantyne and John Groves's third edition as a trainee, bought the fourth edition as a senior registrar, written chapters for Alan Kerr and Philip Stell in the fifth edition, edited the *Basic science* volume of the fifth edition and was ultimately Editor-in-Chief of the seventh edition. As each edition takes about 10 years to produce, that makes me very old indeed. John and Ray have one final task as Editors-in-Chief: to recommend their successors to the publishers. That was made easy for me as both of them had proved themselves more than capable with the previous edition, and the eighth edition is now their masterpiece. They can enjoy the next 10 years as thousands of surgeons worldwide recognize and thank them for their industry.

This edition reflects the continued expansion of our speciality into fields that Scott-Brown himself could never have imagined. It lays the groundwork for the current generation to make their contribution that will, no doubt, be prompted by technological developments, an evidence base of what is wise and what is not, together with the experience gained by teamwork with other clinicians in today's multidisciplinary approach to patient care.

Simply looking at the table of contents it is clear to see that our role in endocrine surgery has increased dramatically over the last 10 years. The thyroid and parathyroids now account for 30 chapters. How would Scott-Brown have viewed that when the tonsils and adenoids justify just one chapter each, and the sore throat has a mere passing reference? Times have certainly changed and ENT surgery has grown up. We have reflected on our past practices, and the evidence base for our management protocols that was emphasized in the previous edition of *Scott-Brown* has been taken to heart.

I hope that this edition will find its way into every medical library in the world and onto every ENT surgeon's bookshelf. It will serve and guide surgeons throughout the English-speaking world, whether they live in high- or low-income countries. It is said that the tragedy of getting old is that we feel young. Reading these volumes makes me wish that I had my time all over again.

Michael Gleeson

Preface

When we were asked to head up the editorial team for this, the eighth edition of *Scott-Brown*, we were mindful of Michael Gleeson's towering achievement in bringing the seventh edition to fruition. Michael delivered a much-loved text – conceived in the early post-war years when antimicrobials, the operating microscope and the National Health Service were all in their infancy – in an entirely new format that befitted modern surgical scholarship. Authors, editors and readers alike had become acutely conscious of the need to quote high-quality evidence to guide clinical decisions; the concept of grading clinical recommendations – and, by implication, acknowledging gaps in the evidence base of our practice – was born. Recognizing the enormity of Michael's contribution led us into the trap that has befallen every editor who has come before us; we grossly underestimated the task ahead. We had misjudged the pace of change. What began as an 'update' of some outdated chapters became a complete rewrite to reflect the advances that marked the decade between editions, but we were determined to keep the text to a manageable size. In the end, we have 330 chapters, but with a slightly smaller page count than the seventh edition.

The basic science knowledge that underpins our clinical practice is no longer focused just on anatomy and physiology; genetics, molecular biology, new techniques for auditory implantation, information technology, new medical therapies for many old disorders together with seismic changes in endoscopic technology and in medical imaging have transformed our specialty. Today's head and neck surgery would have been unrecognizable to the early authors and editors. Surgical oncologists have recourse to completely different treatment strategies than did their predecessors and now work as part of multidisciplinary teams. They deal with different disease patterns and vastly changed patient expectations. Thyroid and parathyroid surgery has become almost exclusively the domain of the otolaryngologist. Surgery of the pituitary fossa has come within our ambit, as has plastic and reconstructive surgery of the head and neck as well as aesthetic facial surgery. Neurotology, audio-vestibular medicine, rhinology and paediatric otolaryngology are accepted subspecialties, each with its own corpus of knowledge and skills and each warranting a sizeable section of this text. Contemporary otolaryngology is now a collection of subspecialty interests linked by common 'stem' training and a shared passion for looking after patients with disorders of the upper respiratory tract and the head and neck.

There is a view that a single text – even a multivolume tome of this size – cannot cover the entire knowledge base of modern clinical practice. The subspecialist will, of course, need recourse to supplementary reading. The pace of change shows no sign of slowing down, but there is still a need for a comprehensive working text embracing the whole spectrum of our workload. That was the task we set our authors and section editors; we think they have done our specialty proud.

In the new 'digital' editorial world authors create manuscripts on personal computers. They transmit chapters, figures, amendments and revisions across continents and time zones with a few keystrokes. The bulky packages containing grainy photographic prints and the reams of paper with closely-typed and heavily scored text that accumulated on authors' and editors' desks are a distant memory. References, guidelines and systematic reviews are all available online; the editorial 'red pen' has been replaced by a cursor on the screen. This 'new age' has enabled us to look ever further for expertise. We are proud to have enlisted the support of authors from more than 20 countries for this edition. *Scott-Brown* always enjoyed particular affection and respect in Asia, Australia, Africa and the Middle East. It has been a joy to welcome authors in increasing numbers from many of these parts of the world. We are now a truly global specialty and the eighth edition fully reflects this.

What has not changed is the huge time commitment authors and editors need to make. That time now has to be fitted into an increasingly pressurized work environment. Revalidation, mandatory training, more intense regulatory scrutiny, expanding administrative burdens and ever-expanding clinical commitments leave little time for scholarship. Our section editors are all busy clinicians. They have generously given their time, first instructing authors, cajoling them and then editing their chapters, virtually all of which have been completely rewritten since the last edition. Each author was chosen because of his or her specific clinical and scientific expertise and none has disappointed. Authors and section editors receive no reward other than the satisfaction of knowing that they have made a contribution to teaching and learning in a specialty that has given us all so much professional satisfaction. We are profoundly grateful to them and hope that their endeavours spur the next generation of otolaryngologists to carry on this noble tradition. *Scott-Brown* simply wouldn't happen without this generous and dedicated commitment, unstintingly and graciously given.

It is impossible to produce a book like *Scott-Brown* without the contribution of many individuals working behind the scenes. We would like to express our gratitude to our Publishers, Taylor and Francis, and to the staff who have worked on this project from its early days in 2011 to publication in 2018. In particular we would like to mention Cheryl Brandt who with good humour and patience helped to reel in many of the 330 chapters. Miranda Bromage joined the team in 2016 and her publishing experience and enthusiasm for medical education have helped guide this new edition through its final phases to publication. Finally, we are indebted to Nora Naughton who has dedicated so much more than just her extensive publishing skills to this project. Nora's meticulous attention to detail, combined with her warmth and wisdom have encouraged us all at the end of this endeavour.

We are truly 'passing on the torch' of a huge amount of accumulated knowledge and wisdom; it is this that gives us, the Editors-in-Chief, the greatest pleasure.

Read on and enjoy, our thoughts are yours.

RWC
JCW

I wish to acknowledge the love, happiness and inspiration that have been passed on to me by both my parents and grandparents. I recognise and value the friendship of my dear friend Ray Clarke who has been with me all the way on this rewarding and worthwhile endeavour. I would specifically like to thank Esme, Helen and William, without whom none of this would have been achievable. Their love and support has helped guide me through the years leading up to the publication of this tome, and my final thanks go to Angela Roberts and Sally Holden for their typing and editing skills.

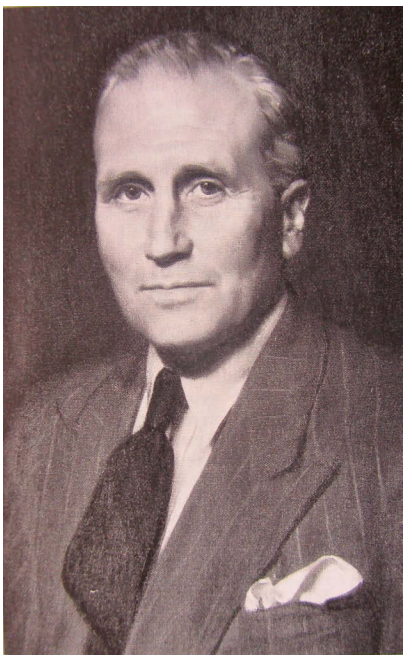
JCW 2018

Thanks to my wife Mary for her patience and support. My parents, Emmet and Doreen Clarke, both sadly died during the preparation of this book. They would have been proud to have played a part in such a scholarly enterprise.

RWC 2018

Black Hut on the River Test – Pastel by W G Scott-Brown – circa 1970. Reproduced by kind permission of Mr Neil Weir, who was presented with the original by the artist.

A Tribute to Bill Scott-Brown



Walter Graham ('Bill') Scott Brown. 1897–1987

Walter Graham ('Bill') Scott-Brown was twenty-three when he arrived at Corpus Christi College Cambridge in 1919. One of the generation of young men whose entry to university and the professions was delayed by their participation in the First World War, he had joined the Gunners in 1915 as an 18-year-old. He considered himself blessed to have survived – although wounded – when so many of his contemporaries never returned from the Front. In those early post-WW1 years the medical school at St Bartholomew's ('Barts') in London was keen to attract 'gentlemen'. To this end a series of scholarships – 'Shuter's scholarships' – was established to lure those with humanities degrees from Oxford and Cambridge into medicine. It was via this scheme that the young Scott-Brown qualified MB, BCh in 1925. By now married to Margaret Bannerman, one of the very few women medical graduates of her generation, the two established a general practice in Sevenoaks, Kent. His work here involved looking after children with poliomyelitis, which was then commonplace, and his MD thesis was on polio-related bulbar palsy. It earned him the Copeman Medal for research from the University of Cambridge. While working in general practice, Bill pursued his interest in the then fledgling specialty of otolaryngology, securing fellowships from London and Edinburgh. Postgraduate training was haphazard; there were no structured programmes or even junior posts, so the young Scott-Brown was fortunate to be awarded a Dorothy Temple Cross Travelling Fellowship. Mrs Florence Temple Cross had set up these awards (now administered by the Medical Research Council) in memory of her daughter, who died in 1927 aged thirty-two. They were made available to young physicians to help them travel to overseas centres specifically to study tuberculosis, then rampant and one of the commonest causes of death in young adults. The young Scott-Brown visited the leading pioneers of the day in Berlin, Vienna, Budapest, Stockholm, Copenhagen, Madrid and Venice. Here he developed his considerable endoscopy skills. He reported that his first bronchoscopies were done on a Venetian street entertainer who, for a few coins, would inhale sundry objects that the doctors would then dexterously retrieve from his main stem and segmental bronchi – without of course any anaesthesia!

Times were lean on Scott-Brown's return. Margaret ('Peggy') was now a popular and well-established GP who supported him as his private practice developed. Eventually he secured appointments at East Grinstead, the Royal National and Royal Free Hospitals. He had a thriving Harley Street practice and was the favoured otolaryngologist of the aristocracy. His reputation was such that he become laryngologist to the Royal family, was appointed Commander of the Victorian Order and was a particular favourite of the then Princess Royal, HRH Mary the Countess of Harewood.

By 1938 he was wealthy enough to purchase a farm in Buckinghamshire where he bred prize-winning shorthorn cattle. Ironmongery and blacksmith work were hard to come by during the war years, so Scott-Brown prided himself on his ability to make his own agricultural implements, cartwheels and farm wagons in a makeshift forge he himself established on the farm. He would while away endless hours here at weekends following a busy week in London. An accomplished fly fisherman, he was part of the exclusive Houghton Club whose members fished the River Test in Hampshire, where he numbered aristocrats including the Prince of Wales among his circle.

Scott-Brown's celebrated textbook came about in the early 1950s, when he became ill with jaundice and heart trouble. He was advised to rest, and took 6 months off work. Not satisfied with editing what has become the standard UK textbook, he took up painting as well. He became a celebrated artist whose work is still prized in many private collections. One of his pastels is reproduced on the preceding page.

Bill Scott-Brown lived to be 90. He died in July 1987, six weeks after his beloved Peggy and just as the fifth edition of the celebrated textbook that still bears his name was going to press. His legacy lives on in the pages of this book, and we are proud to continue the tradition of scholarship and learning which he established all those years ago.

We would like to thank Martin Scott-Brown for his help in compiling the biography above.

John C. Watkinson and Raymond W. Clarke
London, 2018

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Abbreviations

18FDG	18F fluoro-deoxyglucose
3D	three-dimensional
3D-CRT	3D-conformal radiotherapy
5-FU	5-fluorouracil
A	anterior; *or* asthenia
AASM	American Academy of Sleep Medicine
ABC	aspiration biopsy cytology
AC	anterior commissure
ACC	adenoid cystic carcinoma
AcCC	acinic cell carcinoma
ACE	adult comorbidity evaluation; *or* angiotensin converting enzyme
ACNOS	adenocarcinoma not otherwise specified
ACR	American College of Rheumatology
ACTH	adrenocorticotropic hormone
ACV	Acyclovir
AdCC	adenoid cystic carcinoma
ADD	anteromedial displacement of the disc
ADDR	anteromedial disc displacement with reduction
ADL	additive layer manufacture
AECG	American European Consensus Group
AEWD	automatic endoscope washer-disinfector
AF	ameloblastic fibroma
AFD	ameloblastic fibro-dentinoma
AFDS	ameloblastic fibrosarcoma fibro-dentinosarcoma
AFIP	Armed Forces Institute of Pathology
AFO	ameloblastic fibro-odontoma
AFS	ameloblastic fibrosarcoma
AFTER	Adjustment to the Fear, Threat or Expectation of Recurrence
AFX	atypical fibroxanthoma
AgNOR	argyrophilic nucleolar organizer regions
AHA	alpha-hydroxy acid
AHI	apnoea-hypopnoea index
AHNOGB	Association of Head and Neck Oncologists of Great Britain
AHNS	American Head and Neck Society
AIDS	acquired immunodeficiency syndrome
AJCC	American Joint Committee on Cancer
AKs	actinic keratoses
Allo-HSCT	allogeneic hematopoietic stem cell transplantation
ALM	additive layer manufacture; *or* acral lentiginous melanoma
ALS	amyotrophic lateral sclerosis
ALT	alternative lengthening of the telomeres; *or* anterolateral thigh
amBED	acute mucosal BED
ANA	antinuclear anti-bodies
ANCA	anti-neutrophil cytoplasmic antibody
AOT	adenomatoid odontogenic tumour
AP	anterior-posterior
APC	antigen-presenting cell
APPS	anterior parapharyngeal space
ART	anti-retroviral therapy; *or* adaptive head and neck radiotherapy
ASA	American Society of Anesthesiologists
ASHA	The American Speech and Hearing Association
ASSIDS	Assessment of Intelligibility of Dysarthric Speech
ASV	adaptive servo-ventilator
ATLS	advanced trauma life support
ATM	ataxia telangiectasia mutated
ATP	adenosine triphosphate
ATR	ataxia telangiectasia and Rad3-related
ATSG	adjustable tracheostoma valve
ATSV	adjustable tracheostoma valve
AUG	acute ulcerative (necrotizing) gingivitis
AULS	awake unsedated laryngeal surgery
B	breathiness
BAC	basal cell carcinoma
BAHA	bone-anchored hearing aid
BAHNO	British Association of Head and Neck Oncologists
BCC	branchial cleft cyst; *or* basal cell carcinoma; *or* basal cell cancer
BCW	blue collar workers
BD	Bowen's disease
BDD	body dysmorphic disorder
BED	biologically effective dose
BER	base excision repair
bFGF	basic fibroblast growth factor
BHA	beta-hydroxy acid
BKPyV	BK polyomavirus
BLEC	benign lymphoepithelial cysts
BLEL	benign lymphoepithelial lesions

BMI	body mass index
BOT	base of tongue
BP	blood pressure
BTX-A	botulinum toxin type A
BVCMI	bilateral vocal cord mobility impairment
CAD/CAM	computer-aided design/computer-aided manufacture
CAH	clinically assisted hydration
Camp	3',5'-monophosphate; *or* Cyclic AMP
C-ANCA	anticytoplasmic autoantibody
cANCA	cytoplasmic antinuclear cytoplasmic antibody
CAPE-V	Consensus Auditory Perceptual Evaluation of Voice
CAPSO	cautery assisted palatal stiffening operation
CAUP	coblation assisted upper airway procedure
CBCT	cone beam computerized tomography
CBT	carotid body tumour
CBTI	cognitive behavioural therapy for insomnia
CCC	clear cell carcinoma
CCG	clinical commissioning groups
CCI	Charlson comorbidity index
CCOC	clear cell odontogenic carcinoma
CCOT	calcifying cystic odontogenic tumour
CD	Crohn's Disease
CDK	cyclin-dependant kinases
CDKi	cyclin-dependant kinases inhibitors
cDNA	complementary DNA
CEOT	calcifying epithelial odontogenic tumour
CFD	colour-flow duplex doppler
CFTCR	cystic fibrosis transmembrane conductance regulator
CGF	concentrated growth factor
cGVHD	chronic graft-versus-host disease
CH	cluster headache
CHC	Chronic Hyperplastic Candidiasis
CHEP	cricohyodoepiglottopexy
CHOP	cyclophosphamide, doxorubicin, vincristine, prednisolone
CHP	cricohyoidopexy
CI	confidence interval
CICO	can't intubate, can't oxygenate
CIN	cervical intraepithelial neoplasia
CIT	complementary integrated therapies
CLH	cystic lymphoid hyperplasia
CMV	cytomegalovirus
CN	cranial nerve
CNAs	copy number alterations
CNS	clinical nurse specialist; *or* central nervous system
CO_2	carbon dioxide
COAD	chronic obstructive airways disease
COF	cemento-ossifying fibroma
COMT	catechol-O-methyltransferase
COP	clinical outcomes publication; *or* carcinoma of occult primary
COPD	chronic obstruction pulmonary disease
COS	core outcome sets
COSD	Cancer Outcomes and Services Data set
COSMIN	Consensus-based Standards for the selection of Health Measurement Instruments
CPAP	continuous positive airway pressure
CPET	cardiopulmonary exercise training
CPG	central pattern generator
CQx	contact quotient measurement
CRCs	colorectal cancers
CRDS	Cancer Registration Data Set
CRT	chemoradiotherapy
CSA	central sleep apnoea
CSCI	continuous infusion
CSR	Cheyne-Strokes respiration
CSR-CSA	Cheyne-Strokes respiration with central sleep apnoea
CSE	clinical swallowing evaluation
cT	clinical T stage
CT	computed tomography; *or* clinical terms
CTA	computed tomography angiography
CTCAE	common terminology criteria for adverse events
CTLA4	cytotoxic T-lymphocyte-associated protein 4
cTNM	clinical (pre-treatment) classification
C-TORS	cervical-transoral robotic surgery
CTV	clinical target volume
CUP	carcinoma of unknown primary
CW	continuous wave
CXR	chest X-ray
D	dose
DA	desmoplastic ameloblastoma
DAHNO	Data for Head and Neck Oncology
DARS	dysphagia-aspiration risk structures
DAT	digital audiotape
DB	distobuccal
DBCL	diffuse B cell lymphoma
DC	dentigerous cyst
DCF	diced cartilage wrapped in fascia
DCIA	deep circumflex iliac artery
DDR	DNA damage response
DFS	disease-free survival
DFSP	dermatofibrosarcoma protuberans

DGCT dentinogenic ghost cell tumour
DID Diagnositic Imaging Dataset
DIEP deep inferior epigastric perforator
DIGEST Dynamic Imaging Grade of Swallowing Toxicity
DILS diffuse infiltrated lymphocytosis syndrome
DISE drug-induced sedation endoscopy
DM diabetes mellitus
dMRI dynamic MRI
DNSI deep neck space infections
DOI depth of invasion
DR drug resistance
DSA digital subtraction sialography
DSB double-strand break
dsDNA double-stranded DNA
DSI dysphonia severity index
DSS disease-specific survival
DVLA Driver and Vehicle Licensing Authority
DVT deep vein thrombosis
DWI diffusion-weighted imaging
DW-MRI diffusion-weight magnetic resonance imaging

EA early antigen
EAM external auditory meatus
EAT Eating Assessment Tool
EBER Epstein-Barr-encoded RNA
EBNA Epstein-Barr nuclear antigens
EBV Epstein-Barr virus
ECD extracapsular dissection
ECM extracellular matrix
ECS extracapsular spread; *or* extracapsular extension
ED ectodermal dysplasia
EDS excessive daytime sleepiness
EEG electroencephalography
EFS event-free survival
EGF epidermal growth factor
EGFR epidermal growth factor receptor
EGG electroglottographic
EIA enzyme immunoassay
ELG electrolaryngography
ELISA enzyme-linked immunosorbent assay
ELR endoscopic laser resection
ELS European Laryngological Society; *or* electrolaryngeal speech
EM erythema multiforme
EMC epithelial-myoepithelial carcinoma
EMG electromyography
EMR endoscopic mucosal resection
EMST expiratory muscle strength training
EMT epithelial-mesenchymal transition
END elective neck dissection
ENE extranodal extension
ENT ear, nose and throat
EOG electro-oculography
EoO eosinophilic oesophagitis
EOR extra-oesophageal reflux
EORTC European Organisation for the Research and Treatment of Cancer
EPAP expiratory positive airway pressure
EPSCC extrapulmonary small-cell carcinomas
ERAS enhanced recovery after surgery
ERCC1 excision repair cross-complementation group 1
ERCP endoscopic retrograde cholangiopancreatography
ERND extended radical neck dissection
ES oesophageal speech
ESR erythrocyte sedimentation rate
ESS Epworth Sleepiness Scale
ESWL extracorporeal shock wave lithotripsy
ET endotracheal tube
EUA examination under anaesthetic
EUS endoscopic ultrasound
EVT Estill Voice Training
EXIT ex utero intrapartum treatment

FA Fanconi's anaemia
FAMM facial artery myomucosal flap
FBC full blood count
FD fibrous dysplasia
FDA Food and Drug Administration
FDG fluorodeoxyglucose
FDG-PET fluorodeoxyglucose positron emission tomography
FEES functional endoscopic evaluation of swallowing
FEESST flexible endoscopic evaluaton of swallowing with sensory testing
FESS functional endoscopic sinus surgery
FEV_1 forced expiratory volume in one second
FFPE formalin-fixed paraffin embedded
FFT fast Fourier transform
FGD fluorodeoxyglucose
FISH fluorescence *in situ* hybridization
FISS fast-interrupated steady state
FK Feyh-Kastenbauer
FLIM fluorescence lifetime imaging
fMRI functional magnetic resonance imaging
FNA fine-needle aspiration
FNAB fine-needle aspiration biopsy

FNAC fine-needle aspiration cytology
FOIS functional oral intake scale
FONA front of neck airway
FoR fear of recurrence
FS Frey's syndrome
FTA-abs fluorescent treponemal antibody absorbed test
FTSG full-thickness skin grafts
FVC forced vital capacity

G glucose; *or* grade
GA general anaesthesia; *or* glycolic acid
GAN greater auricular nerve
GAS group A streptococcus
GBI Glasgow Benefit Inventory
GCS Glasgow coma scores
G-CSF granulocyte colony stimulating factor
GERD gastro-oesophageal reflux disease
GF growth factor
GFR growth factor receptors
GI gastrointestinal
GMC General Medical Council
GM-CSF granulocyte-macrophage colony-stimulating factor
GORD gastro-oesophageal reflux
GPA granulomatosos with polyangiitis
GPU gastric pullup
GRBAS grade, roughness, breathiness, asthenia, strain
GSW gunshot wound
GTV gross tumour volume
GVHD Graft Versus Host Disease

HA hyaluronic acid
HA/ALG hyaluronic acid/mildly cross-linked alginate
HAART highly active antiretroviral therapy
hAdMSCs human adipose-derived MSCs
HANA Head and Neck Audit
HCV hepatitis C virus
HDTV high-definition television
HDU High Dependency Unit
H&E haematoxylin and eosin
HEM heat and moisture exchanger
HES hospital episode statistics
HGF hepatocyte growth factor
HGT high-grade transformation
HHV-8 human herpes virus 8
HIV human immunodeficiency virus
HL Hodgkin lymphoma
HLA human leucocyte antigen
HNC head and neck cancer
HNR harmonics-to-noise ratio
HNSCC head and neck squamous cell carcinoma
HP hyperparathyroidism
HPF high power fields
HPV human papillomavirus
HQIP Healthcare Quality Improvement Partnership
HR homologous recombination; *or* heart rate
HRHPV high-risk human papillomavirus
HRM high-resolution manometry
HRQOL health-related quality of life
HSPL horizontal supraglottic partial laryngectomy
HSV herpes simplex virus
hTERT human telomerase reverse transcriptase expression
HTLV-1 Human T-lymphocytic virus 1
hVFFs human vocal fold fibroblasts
Hz Hertz

I inferior
IBD inflammatory bowel disease
IC induction chemotherapy
ICD International Classification of Disease
ICD-O International Classification of Diseases for Oncology
ICF HNC International Classification of Functioning, Disability and Health for head and neck cancer
ICIDH International Classification of Impairment Disabilities and Handicaps
ICON-S International Collaboration on Oropharyngeal cancer and Network for Staging
ICRT induction chemotherapy followed by radiation
ICS immunochromatographic strip
ICSD international classification of sleep disorders
ICU Intensive Care Unit
IFN-a interferon alpha
IFN-g interferon-g
IgA immunoglobin A
IgG immunoglobulin G
IGRT image-guided radiotherapy
IHC immunohistochemistry
IHNSG International Head and Neck Scientific Group
IJV internal jugular vein
IL-1 interleukin-1
IM infectious mononucleosis
IMPT intensity-modulated proton beam therapy
IMRT intensity-modulated radiotherapy
IOPI Iowa Oral Performance Instrument
IOSGT intra-osseous salivary gland tumours

IPAP inspiratory positive airway pressure
IP-SDM inter-professional shared decision-making
IRIS immune reconstruction inflammatory syndrome
ISH *in situ* hybridization
ISS idiopathic subglottic stenosis
IV intravenous
IVIM intravoxel incoherent motion

KCOT keratocystic odontogenic tumour
KD Kikuchi disease
KFI Kaplan-Feinstein index
KS Kaposi sarcoma
KSHV Kaposi sarcoma-associated virus
KTP potassium titanyl phosphate
KWD Kawasaki disease

L lateral; *or* lower
LADD lacrimal-auriculo-dentodigital
LAUP laser-assisted uvulopalatoplasty
LCH Langerhans cell histiocytosis
LCT long-chain triglycerides
LD laryngeal dysplasia
LDH lactic dehydrogenase
LEMG laryngeal electromyography
LENT SOMA late effects of normal tissue
LFT liver function tests
LGB labial gland biopsy
LMM lentigo maligna melanoma
LMN lower motor neurone
LMRVT Lessac-Madsen Resonant Voice Therapy
LMT laryngeal manual therapy
LOH loss of heterozygosity
LOS lower oesophageal sphincter
LP laryngeal preservation; *or* lichen planus
LPC linear predictive coding
LPR laryngopharyngeal reflux
LRC locoregional control
LSCC laryngeal squamous cell carcinoma
LSE London Speech Evaluation
LSVT Lee Silverman Voice Therapy
LTAS long-term average spectrum
LTB laryngotracheobronchitis
LTR laryngotracheal reconstruction
LTS laryngotracheal stenosis
LVE lymphovascular emboli

M medial; *or* meta-static sites
MAB monoclonal antibodies
mAbs monoclonal antibody drugs
MACH-NC meta-analysis of chemotherapy in head and neck cancer
MAC-NPC meta-analysis of chemotherapy in nasopharyngeal carcinoma
MAGIC MRC adjuvant gastric infusional chemotherapy
MAMS multi-arm-multi-stage
MAPK mitogen activated protein kinase
MAS mandibular advancement splints
MB multibacillary; *or* mesiobuccal
MBS modified barium swallow
MBSImp Modified Barium Swallow Impairment Profile
MC mentocervical
MCC Merkel cell carcinoma
MCII multichannel intraluminal impedance
MCT medium-chain triglyceride
MDADI MD Anderson Dysphagia Inventory
MDR multiple drug resistance
MDSCs myeloid-derived suppressor cells
MDT multidisciplinary team
MEC mucoepidermoid carcinoma
MEK MAPK/extracellular signal related kinase
MEN multiple endocrine neoplasia
MEN-2A multiple endocrine neoplasia syndrome type A
MEP motor-evoked potential
MFR mean airflow rate
MG myasthenia gravis
MGG May-Grunwald-Giemsa
MIO minimally invasive oesophagect
MIP maximum intensity projection
miRNA microRNA
MiSG minor salivary glands
MiSGC minor salivary gland cancer
MIVAT minimally invasive video-assisted thyroidectomy
MLST multiple sleep latency test
MLT micro-laryngoscopy tubes
MMC Mitomycin-C
MMR measles, mumps and rubella
MND motor neurone disease
MPNT malignant peripheral nerve sheath tumour
MPT maximal phonation time
MPTP 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
MR magnetic resonance
MRA magnetic resonance angiography
MRC Medical Research Council
MRD marginal reflex distance
MRI magnetic resonance imaging
MRND modified radical neck dissection
MRSA methicillin-resistant *Staphylococcus*

MS median survival
MSA multiple system atrophy
MSC mesenchymal stem cells
MSFo mean speaking fundamental frequency
MSG minor salivary glands
MSLT Multiple Sleep Latency Test
MSM men who have sex with men
MST malnutrition screening tool
MTC medullary thyroid carcinoma; *or* medullary thyroid cancer
MTD muscle tension dysphonia
MUST Malnutrition Universal Screen Tool
MV megavolts
MWT maintenance of wakefulness test

N nodes
NBCCS naevoid basal cell carcinoma syndrome
NBF neutral buffered formalin
NBI narrow band imaging
NBM nil by mouth
NCC nasopharyngeal cancer
NCDB National Cancer Data Base
NCEPOD National Confidential Enquiry into Perioperative Deaths
NCI National Cancer Institute
NCIN National Cancer Intelligence Network
NCRAS National Cancer Registration and Analysis Service
NCWTMDS National Cancer Waiting Times Monitoring Data Set
Nd : YAG neodymium-doped yttrium aluminium garnet
NEED nose, ear, eye and temple
NERD non-erosive reflux disease
NF nasofrontal
NF1 neurofibromatosis type 1
NFc nasofacial
NGF nerve growth factor
NGT nasogastric tube
NHANES National Health and Nutrition Examination Survey
NHEJ non-homologous end-joining
NHL non-Hodgkin lymphoma
NHS National Health Service
NICE National Institute for Clinical Excellence
NK natural killer cells
NM nasomental; *or* nodular melanoma
NMSC non-melanoma skin cancers
NNE normalized noise energy
NNTB number needed to treat to benefit
NOS not otherwise specified
NPC nasopharyngeal carcinoma; *or* nasopharyngeal cancer
NRA nucleus retroambigualis
NRCS National Cancer Registration System
NSAIDs non-steroidal anti-inflammatory drugs
NT nasal length
NTAM non-tuberculosis atypical mycobacteria
NTL near total laryngectomy
NTLP near total laryngectomy with partial pharyngectomy
NTM non-tuberculosis atypical mycobacteria
NZIMES New Zealand Index for Multidisciplinary Evaluation of Swallowing

OAN olfactory neuroblastoma
OCC oral cavity carcinoma; *or* oral cavity cancer
OCT optical coherence tomography
ODI oxygen desaturation index
OF ossifying fibroma; *or* odontogenic fibroma
OFG oto-facial granulomatosis
OFM odontogenic fibromyxoma
OGD oesophagogastroduodenoscopy
OHL oral hairy leukoplakia
OHS obesity hypoventilation syndrome
OI osteogenesis imperfecta
OM odontogenic myxoma
OME otitis media with effusion; *or* oral motor exercise
OMFS oral and maxillofacial surgery
ONS Office for National Statistics
OPC oropharyngeal candidiasis; *or* oropharyngeal carcinoma
OPCS Office for Population Censuses and Surveys
OPG orthopantomogram
OPL open partial laryngectomy
OPSCC oropharyngeal squamous cell carcinoma
OPSE oropharyngeal swallow efficiency
ORF open reading frames
ORL-HNS otorhinolaryngology – head and neck surgery
ORN osteoradionecrosis
OS overall survival
OSA obstructive sleep apnoea
OSAH obstructive sleep apnoea/hypopnoea
OSAHS obstructive sleep apnoea/hypopnea syndrome
OSAS obstructive sleep apnoea syndrome
OSNA One Step Nucleic acid Amplification

P posterior; *or* palatal
PA peripheral (extra-osseous) ameloblastoma
PAA posterior auricular artery

PAC polymorphous adenocarcinoma; *or* parathyroid carcinoma
$PaCO_2$ partial pressure carbon dioxide
PaO_2 partial pressure oxygen
PAG periaqueductal grey matter
PANDAS pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections
PAL physical activity level
PARP polymerase
PAS Periodic acid-Schiff
PB paucibacillary
PB-MDT paucibacillary multidrug therapy
PBP progressive bulbar palsy
PCA posterior cricoarytenoid
PCF pharyngocutaneous fistulae
PCI Patient Concerns Inventory
PCL polycaprolactone
PCNA proliferating cell nuclear antigen
PCR polymerase chain reaction
PCU palliative care unit
PD Parkinson's disease
PD1 programmed death 1
PD-L1 programmed death ligand 1
PDT photodynamic therapy
PE pharyngo-oesophageal
PEG percutaneous endoscopic gastrostomy
PES pharyngeal electrical stimulation; *or* progressive elevation of oesophageal pressure
PET positron emission tomography
PET-CT positron emission tomography/computed tomography
PFS progression-free survival
PGL persistent generalized lymphadenopathy
PG-SGA patient generated SGA
PHA polyhydroxy acid
PIOSCC primary intra-osseous squamous cell carcinoma
PIP peak inspiratory pressure
PKB protein kinase B
PLAG1 pleomorphic adenoma gene 1
PLGA polymorphous low-grade adenocarcinoma
PLMD periodic limb movement disorder
PLMS periodic limb movement syndrome
PLS primary lateral sclerosis
PMA progressive muscular atrophy
PMMC pectoralis majory myocutaenous
PNET primitive neuroectodermal tumour
PNI perineural invasion
PNS peripheral nervous system
PORCT post-operative CRT
PORT post-operative radiotherapy
POST post-operative radiotherapy
PPI proton pump inhibitor
PPPS posterior parapharyngeal space
PPS parapharyngeal space
PPV positive predictive value
pRb retinoblastoma protein
PROs patient-reported outcomes
PROMs patient-reported outcome measures
PRSA post-streptococcal reactive arthritis
PRV planning risk volume
PS performance status; *or* pyriform sinus
PSA pleomorphic salivary adenoma
PSG polysomnography
PSGN post-streptococcal glomerulonephritis
PSP progressive supranuclear palsy
PSSHN performance status scale for head and neck
pT pathological T stage
PTA peritonsillar abscess
PTC papillary thyroid cancer
pTNM pathological (post-surgical histopathological) classification
PTV planning target volume

QOL quality of life
qRT-PCR quantitative reverse transcription – polymerase chain reaction

R roughness
RAD radiation-associated dysphagia
RADT rapid antigen detection tests
RARs retinoic acid receptors
RAS reticular activating system
RB retinoblastoma protein
RB1CC1 RB1-inducible coiled-coil 1
RBC red blood cell
RBD REM behaviour disorder
RCR Royal College of Radiologists
RCSLT Royal College of Speech & Language Therapists
RCT randomized controlled trials
RDI respiratory disturbance index
REM rapid eye movement
RERA respiratory effort-related arousals
RF rheumatoid factor
RFA radiofrequency ablation
RFS reflux finding score
RIG radiological inserted gastrostomy
RIS radiation-induced sarcoma
RLN recurrent laryngeal nerve
RLS restless legs syndrome

RMT retromolar trigone
RNA ribonucleic acid
RNA-ISH RNA-based chromogenic *in-situ* hybridization
RND radical neck dissection
ROOF retro-orbicularis oculi fat
ROS reactive oxygen species
RP rapid prototyping
RPR rapid plasma reagin test
RR relative risk; *or* risk ratio
RSI reflux symptom index
RT radiotherapy; *or* radiation therapy
RTA road traffic accident
RTDS Radiotherapy Data Set
RTKs receptor tyrosine kinases
rTMS repetitive TMS
RTOG Radiation Therapy Oncology Group
RTOG-EORTC Radiation Therapy Oncology Group-European Organisation for the Research and Treatment of Cancer
rt-PCR (real-time) polymerase chain reaction
RTPG radiation therapy oncology group
RXRs retinoid X receptors

S superior; *or* synthesis; *or* strain
SACT systemic anti-cancer therapy
SAI supraclavicular artery island flap
SANS subacute necrotizing sialadenitis
sBCC superficial basal cell carcinoma; *or* second branchial cleft cyst
SC sebaceous carcinoma
SCC squamous cell carcinoma
SCCHN squamous cell carcinoma of the head and neck
SCM sternocleidomastoid
SCPL supracricoid partial laryngectomy
SD spasmodic dysphonia
SDC salivary duct carcinoma
SDH succinyl dehydrogenase
SDM shared decision-making
SE sialoendoscopy
SEER Surveillance Epidemiology and End Results
sEMG surface electromyography
SFF speaking fundamental frequency
SFRPs secreted frizzled-related proteins
SGA Subjective Global Assessment
SGC salivary gland carcinoma
SHI Speech Handicap Index
SI signal intensity
SIGN Scottish Intercollegiate Guidelines Network
SIL squamous intraepithelial neoplasia
SLAD–R selective laryngeal adductor denervation–reinnervation surgery
SLE systemic lupus erythematosus
SLN superior laryngeal nerves
SLNB sentinel lymph node biopsy
SLP speech language pathologists; *or* superficial lamina propria
SLS sodium lauryl sulphate
SLT speech and language therapist
SM stomium to menton
SMA solid/multicystic ameloblastoma
SMAS superficial musculoaponeurotic system; *or* subcutaneous musculo aponeurotic system
smTKI small molecule tyrosine kinase inhibitors
SNAP synaptosome associated protein
SNB sentinel node biopsy
SND selective neck dissection
SNE sleep nasendoscopy
SNOMED Systemised Nomenclature of Medicine
SNR signal-to-noise ratio
SNUC sinonasal undifferentiated carcinoma
SO sclerosing osteomyelitis
SOOF suborbicularis oculi fat
SOREM sleep onset REM
SOT squamous odontogenic tumour
SOVT semi-occluded vocal tract therapy
SPECT single-protein emission computed tomography
SPL sound pressure level
SRBD sleep-related breathing disorder
SRI serotonin re-uptake inhibitors
SS Sjögren's syndrome
SSB single-strand break
ssDNA single-strand DNA
SSM superficial spreading melanoma
SSQ Sydney Swallow Questionnaire
SSRI selective serotonin reuptake inhibitor
STA superficial temporal artery
STIR short tau inversion-recovery; *or* short time inversion recovery
STL salvage total laryngectomy
SToPS tracheoesophageal voice auditory-perceptual tool
STPL supratracheal partial laryngectomies
STS split thickness skin grafts; *or* soft tissue sarcoma
STSG split-thickness skin grafts
SUR salivary gland-to-background uptake ratio
SUV standard uptake value
SVR surgical voice restoration
SWAL-QoL swallow-specific Quality of Life questionnaire

T tumour; *or* time
TANIS T and N integer score
TB tuberculosis
TBM tongue base mucosectomy
TCA trichloroacetic acid peel
TCGA The Cancer Genome Atlas
TDC thyroglossal duct cyst
tDCS transcranial direct current stimulation
TdT terminal deoxynucleotidyl transferase
TE tracheo-oesophageal
TEE total energy expenditure
TENS transcutaneous electrical nerve stimulation
TEP tracheo-oesophageal puncture
TGF transforming growth factor
TIC time-intensity curves
TILs tumour infiltrating lymphocytes
TKI tyrosine kinase inhibitors
TL total laryngectomy
TLM transoral laser microsurgery
TLPE total laryngo-pharyngo-oesophagectomy
T-max time to maximum contrast enhancement
TMD temporomandibular disorders
TMJ temporomandibular joint
TMS transcranial magnetic stimulation
TN trigeminal neuralgia
TNE transnasal (o)esophagoscopy
TNM tumour, node, metastasis
TNO transnasal oesophagoscopy
TOLS transoral laser surgery
TORS transoral robotic surgery
TOS transoral surgery
TOVS transoral videoendoscopic surgery
TPF temporoparietal fascia
TPHA *T. pallidum* haemagglutination assay
TPPA *T. pallidum* particle agglutination assay
TRAF TNF receptor associated factor
TSG tumour suppressor gene
TSH thyroid-stimulating hormone
TSP tumour suppression protein
TTA thermal-tactile application
TTLRR time to local-regional recurrence
TVC true vocal cord

U upper
UA unicystic ameloblastomas
UADT upper aerodigestive tract
UARS upper airways resistance syndrome
UC ulcerative colitis
UgFNAC ultrasound guided fine-needle aspiration biopsy
UGCB ultrasound-guided core biopsies
UICC Union for International Cancer Control
UMN upper motor neurone
UOS upper oesophageal sphincter
UPPP uvulopalatopharyngoplasty
US ultrasound
USA United States of America
US-FNAC ultrasound-guided FNAC
USG ultrasonography
USgFNAC ultrasound-guided fine-needle aspiration cytology
USS ultrasound scanning
UV ultraviolet
UW-QOL University of Washington Quality of Life Questionnaire

VA Veterans Affairs
VAPP Voice Activity and Participation Profile
VAS visual analogue scale
VC vocal cord; *or* verrucous carcinoma
VCA viral capsid antigen; *or* vascularized composite allografts
VDRL Venereal Disease Research Laboratory
VEGF vascular endothelial growth factor
VF videofluoroscopy
VFE vocal function exercises
VFSS videofluoroscopic swallowing study
VHI Voice Handicap Index
VHi-10 Vocal Handicap Index 10 item questionnaire
VMAT volumetric modulated arc therapy
VoiSS Voice Symptom Scale
VPA Voice Profile Analysis
VPQ Vocal Performance Questionnaire
VRP voice range profile
VR-QOL voice-related quality of life
VVI Vocal Velocity Index

WCC white cell count
WDTC well-differentiated thyroid cancers
WES whole exome sequencing
WG Wegener's granulomatosis
WGS whole genome sequencing
WHO World Health Organization
WST water swallow test
WUHNCI Washington University Head and Neck Co-morbidity Index

XQ xerostomia-specific questionnaire

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CHAPTER 1

HISTORY

Patrick J. Bradley

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SEARCH STRATEGY

Data in this chapter may be updated by a PubMed search using the keywords: head and neck surgery, head and neck cancer, head and neck neoplasms and history of head and neck cancer.

INTRODUCTION

The pace of change in the treatment of head and neck tumours has accelerated since the 1950s with a remarkable transition from predominantly ablative surgery to combined therapies focused on preservation of the form and function of the anatomic structures of the head and neck. This chapter will summarize the history of head and neck surgery, with information gleaned from published summaries of this history and original articles.[1–9]

The term 'head and neck surgery' dropped into obscurity from 1906 until 1948, when Hayes Martin used it in one of his early papers.[10] In the same year, Grant Ward published an editorial[11] which defined the future parameters of this 'new' surgical specialty.[9, 10] This surgical discipline was progressed by several groups of surgeons which included Grant E. Ward and James W. Hendrick (1901–1992) of Johns Hopkins Hospital in the United States, who published of their extensive experience in caring of head and neck cancer patients in *Tumors of the Head and Neck in 1950*,[12] with Sir Stanford Cade (1895–1973) General Surgeon and Radiotherapist, Westminster Hospital, Arthur John Gardham (1899–1983) General Surgeon, William Douglas Harmer (1873–1962), Otolaryngologist and Radiotherapist, St Barts. Hospital, Ronald William Raven (1904–1992), General Surgeon and Radiotherapist, St Barts. Hospital and others in Britain, and Henri Redon (1899–1974), Paris and Georges Portmann (1890–1985), Bordeaux who are to be credited with the formation of modern head and neck surgery.[13]

THE MIDDLE AGES

Some of the earliest attempts at head and neck surgery can be credited to Egyptian physicians who attempted ablative and reconstructive procedures of the oral cavity and lip. The 'Edwin Smith Papyrus' (named after the dealer, an American Egyptologist who bought it in 1862), the origins of which are dated at 3000–2500 BCE, contains some of the first descriptions of surgical management of mandibular and nasal fractures, as well as lip tumours.

Arguably, the first documented efforts of reconstructive head and neck surgery are found in the Sanskrit texts of ancient India written approximately 2600 years ago. During this period of Indian history, reconstructive surgery of the nose and ear was highly valued, as invaders from surrounding territories would often stigmatize their victims by amputating the nose or ear. Contained within the publication of Sushruta Samhita (Sushruta's compendium), an ancient Sanskrit text on medicine and surgery, are described numerous surgical techniques for the reconstruction of head and neck defects, dating from the mid-first millennium BCE. Sushruta, regarded as the 'father of Indian surgery', described a variety of pedicle and rotation flaps, similar to many of the techniques utilized in the nineteenth and twentieth centuries. He is reasonably considered the pioneer of reconstructive nasal surgery, having described more than 15 different methods.[14]

Whether Hellenistic or Roman physicians were exposed to the Indian techniques through Alexander the Great's expedition to India in the 4th century BCE is debatable.

Certainly, Roman and Hellenistic physicians described similar techniques to those described in India. Aulus Cornelius Celsus, (c. 25 BC–c. 50 AD), considered to be the greatest of the Roman medical authors and surgeons, also described a variety of techniques similar to those practised in India in his medical text of the 1st century, *De Medecina*, and is credited with one of the first head and neck cancer procedures describing excision of a lip malignancy.[15]

After the fall of Rome in the 5th century and the diffusion of Barbarians and Christianity throughout the Middle Ages, a significant decline in the advancement of all surgery, in particular reconstruction, occurred. This decline was certainly aided by Pope Innocent III (1160b: 1198–1216d Papal Reign), who prohibited surgical procedures of all types. It is interesting to note that physicians of the time considered surgery to be a manual skill and below their intellectual and societal stature. Physicians tended to be academics, working in universities, and mostly dealt with patients as an observer or consultant. Thus appeared the concept of the barber surgeon, and the decline of the role of surgery and surgeons ensued. Despite this, surgery of the head and neck was practised and developed in the Middle Ages but documentation of this is scarce.[16]

The period of Renaissance in the 14th century signalled a rebirth of science, medicine and surgery. In 1442, the Branca family gained prominence in the field of wound reconstruction and, in particular, they reintroduced the previously described Indian methods of nasal reconstruction, using cheek and forehead flaps.[17] Branca's son Antonius modified this technique developing the use of a delayed skin flap donated from the arm. This Italian method, as it became known, was eventually learned by other surgical dynasties (surgical practice at this time in Italy was very much a family affair). Prominent examples include Gasparro Tagliacozzi's (1546–99) work around nasal reconstruction, also using skin donated from the arm. It is believed that Tagliacozzi learned his surgical techniques from members of the Vianeo family from Calabria. Following his own work, he is credited with making significant contributions to facial reconstructive surgery describing and refining the use of distant pedicled flaps for a variety of head and neck reconstructions.[18]

PRE-20TH CENTURY

Oral cavity surgery

Pimpernelle, in 1658, is reported to have been the first who employed a hemiglossectomy to treat macroglossia caused by mercury administration,[1] whilst Marchetti (1589–1673) is credited with the first surgical removal of a malignant tumour of the tongue in 1664.[19] The first published description of a case of lingual cancer was made some 30 years earlier by an Englishman, Alexander Reade (1586–1641), in 1635.[20]

Surgical haemorrhage was a major limitation in the development of head and neck surgery. Accordingly, Germanicus Mirault (1796–1879) in 1813 and Konrad Johann Martin Langenbeck (1766–1851) in 1819 described the ligation of the lingual artery or the use of haemostatic sutures before proceeding with tongue surgery, in an attempt to reduce likelihood of death from exsanguination.[3, 6] A further advance in haemostasis was made by Albretch Middledorpf (1824–68) in 1834, who introduced the galvanic cutting current, the first description of cutting diathermy, to reduce surgical bleeding during incision. Developing this theme, the meticulous approach to haemostasis during surgical dissection proselytized by Emil Theodor Kocher (1841–1917) became the accepted surgical approach throughout the world.[4]

The intra-oral route of excision of tongue lesions was recognized as inadequate for more complicated and advanced tumours and therefore new, open surgical approaches were developed to enhance surgical exposure of lesions of the oral cavity; Joseph H Cloquet (1787–1840) in 1827 and Giorgio Regnoli (1797–1859) in 1838, both Italians used the suprahyoid route to improve access to the base of tongue;[4] Theodor Billroth (1829–94) and Vincenz Czerny (1842–1916) further modified this approach, describing the addition of lateral vertical incisions to the transverse suprahyoid incision. Regnoli went further, describing a retrograde 'pull-through' technique, which was later popularized in the 1860s. However, it was Philibert Joseph Roux (1780–1854) (France) in 1836, followed by James Syme (1799–1870) (Scotland) and Billroth, who described the precursor approach of the lip-split mandibulotomy, which is still commonly used in contemporary head and neck surgical practice, whereby the lip initially is incised in the midline and, deep to this, the mandible is incised through the symphysis, allowing the retraction of the mandibular rami to gain unfettered access to the oral cavity and oropharynx. In 1875, using a variation of the theme, Bernard Rudolf Konrad von Langenbeck (1810–87) divided the mandibular ramus opposite the first molar tooth and ligated the underlying lingual artery prior to removing the enlarged regional lymph nodes in addition to the primary tumour sited in the base of the tongue. Access to the oral cavity from the neck following the raising of a superiorly based musculocutaneous flap as developed by Billroth (1829–1894) of Vienna, was further modified by Kocher of Bern.[20] By the turn of the century Henry Trentham Butlin (1843–1912)[21] and Anton Wolfler (1890–1917) (a member of Billroth's surgical school) had refined the final approaches that established future surgical approaches to the oral cavity, removal of the primary lesion with its regional lymph nodes.[3, 4]

Laryngeal surgery

Visualization of the larynx in life, prior to the invention of the laryngoscope, was not a trivial matter.

An inspection device using mirrors and candles or sunlight for illumination was devised during the early part of the 1800s and almost perfected by John Avery (1807–55), a surgeon at Charing Cross Hospital, London, in 1848 and by Ephraim Cutter (1832–1917) of Boston around 1858. However, Manuel Patricio Rodriguez García (1805–1906),

a Professor of Singing at the Paris Conservatoire who had settled in London, is widely accredited as the first person to view the larynx (his own) in a living human using two mirrors and the sun as a light source.[22] The first clinical application of the indirect laryngoscope was made by Ludwig Turck (1810–68), a neurologist from Vienna, around 1858. By the early period of the 1860s Georg Richard Lewin (1820–96) declared that he had seen more than 60 cases of laryngeal neoplasms and performed surgery using either cutting devices or caustics.[7]

On 23 April 1895 in Berlin, Alfred Kirstein (1863–1922) performed the first direct laryngoscopy, using a modified oesophagoscope.[23] Despite the limitation in visualizing the larynx – and in particular the functioning larynx – there have been a number of reports of larynx tumours being removed 'per viam naturalis'. In 1770, G Koderik, a surgeon in Brussels, reported the ligation of a laryngeal polyp by a snare device. Moreover, the operation of cricothyrotomy and thyrohyoid laryngectomy were devised by French surgeons Felix Vicq d'Azyi (1748–1794) in 1776 and Joseph-François Malgaigne (1806–1865) in 1850 respectively. The first laryngofissure, credited to Ludolph Brauers (1865–1951) of Louvaine in 1833 which was performed without a covering tracheostomy. Laryngofissure was performed under chloroform anaesthetic by Gordon Buck (1807–77) in the United States in New York in 1851, and in London, England by Sir George Duncan Gibb (1821–76) in 1864.[7, 8]

The London laryngologist Morell Mackenzie,[3, 24] (1837–92), having been trained in Vienna and Budapest under Johann Czermak (1828–73), commenced practice in 1862 and is considered the father of British laryngology. As the first English laryngologist, he was the founder of the first hospital for diseases of the throat in the world, which opened in London in 1865. Among Mackenzie's succession of assistants at Golden Square were Lennox Browne (co-founder of the British Rhino-Laryngological Association), Gordon Holmes (author of the first history of laryngology), Felix Simon (Semon's Law), Grenville Macdonald (Professor of Laryngology, King's College Hospital), Norris Wolfenden (co-founder of The Journal of Laryngology and Otology), John Nolan Mackenzie (of Johns Hopkins Hospital), Samuel Johnston (Surgeon to the Baltimore Eye, Ear and Throat Charity Hospital and one of the founders of the American Laryngological Association), Charles Louis Taylor (subeditor of the British Medical Journal), James Donelan (the first laryngologist at the Italian Hospital) and Mark Howell (who assisted during the treatment and attended until the death of Emperor Frederick III June 1888).[7]

The first total laryngectomy was performed by Professor Theodor Billroth (1829–94) of Vienna on 30 December 1873, having excised a laryngeal tumour via a thyrotomy incision, preserving the right vocal cord some weeks earlier. The patient died of local recurrence 7 months following his major surgery. The last success on record was achieved by Enrico Bottini (1837–1903), of Turin. The long survivor was achieved for 15 years after total laryngectomy performed in 1875. Jacob da Silva Solis-Cohen (1838–1927) was the first, in 1884, to perform a total laryngectomy in America – the patient survived 11 years without a recurrence. Based on his contribution to the discipline, it has been proposed that Solis-Cohen be acknowledged as America's first head and neck surgeon.[25]

Paranasal sinuses and nasopharynx surgery

The first total maxillectomy was reportedly performed in 1827 in Lyon, by Joseph Gensoul (1797–1858) without anaesthesia. With further practice, it was said that Gensoul perfected his technique and could complete the procedure in two-and-a-half minutes. A variety of incisions have been suggested over time by various surgeons including Alfred Velpeau (1807–73) of Paris, Karl Otto Weber (1827–67) from Frankfurt, Sir William Ferguson (1808–77) and Thomas Tatum (1802–1879) of London, and James Syme (1799–1870) of Edinburgh. Auguste Nelaton (1807–73) of Paris promoted a transpalatal approach to the nasopharynx in 1859, whilst Pierre Charles Huguier (1804–73), also of Paris, advocated a transmaxillofacial or lateral nasal approach. In 1902, Emil-Jules Mourne (1855–1914) of Bordeaux, published his 'lateral rhinotomy' approach and Alfred Denker (1863–1941) in 1905 described a sublabial approach to the nasal cavity and maxillary antrum.[8]

THE 20TH CENTURY

Following the death of Pimpernelle, in the mid-17th Century, an interval of almost 200 years passed during which it appears from the absence of historical evidence that the development of surgery of the head and neck stagnated.[1] The reasons for lack of significant progress related to the lack of what are now considered fundamental needs for any surgery, such as general anaesthesia, antiseptic techniques, blood banking, antibiotics, surgical pathology and skilled nursing care. The discovery of anaesthesia occurred in the 1840s: ether in 1842; nitrous oxide in 1844; and chloroform in 1847. Local anaesthetic in the form of cocaine was not discovered until 1880.

The introduction of binocular operating microscope heralded the possibility of performing microsurgery of the larynx and other sites. The principal changes in endoscopy have occurred since the 1950s and have been associated with technical improvements in lighting, magnification and instrumentation as well as documentation of clinician findings. Harold Hopkins (1918–94) and Narinder Singh Kapany (b.1926) developed and subsequently introduced the rigid and flexible fibreoptic systems in 1954.[26] Harold Hopkins' solid rods, with their different angles connected to a proximal light source by a fibreoptic cable, have become essential tools for diagnostic and therapeutic procedures in the head and neck. Fibreoptic light sources aided both rigid endoscopy and the flexible fibrescopes, introduced in 1957, allowed improved visualization of the mucosal head and neck subsites and the early detection and diagnosis of cancer in the awake patient. Advancement in pathology, radiology and radiotherapy have expanded the 'team approach' to improve the patient's diagnosis, improved staging of disease

and expanded the options available for the management of patients with head and neck cancer.

Head and neck pathology

The modern era was heralded by the development of the achromatic microscope, which allowed pathologists to first view tissues under magnification.[1, 27] The mid-19th century was dominated by developments in the pathologic description of tumours, including those by the father of modern oncologic pathology, Rudolf Virchow (1821–1902).[28] Virchow, the pioneer of cellular pathology, published the first study of the pathology of tumours in 1858. Surgical pathology, however, only began to develop as a distinct specialty from the 1960s onwards. Two fundamental concepts regarding head and neck cancer were published by Albert C Broders (1885–1964) of the Mayo Clinic in the early 1920s. First, he defined the grading system of squamous cancer of the lip,[29] and subsequently applied it to sites of the head and neck.[30] Broders also described carcinoma *in situ*, although the topic was more firmly established by a subsequent detailed report by John D Crissman and Richard J Zarbo in 1989.[31] Several of the early head and neck surgeons were also experienced pathologists: Joseph H Ogura (1915–83), Barnes Hospital, and John J Conley (1912–99), New York checked their own frozen sections during the weekends.[32] John A Kirchner (1915–2011), Yale, performed serial sections of 100 total laryngectomy specimens in his search for the anatomical pathways by which laryngeal cancer spread.[33] It was at the Centennial Conference on Laryngeal Cancer in 1974 (100 years after the death of Billroth) that the first public interaction between surgeons and pathologists took place and a new era of working practices was established.[34] The appointment of Vincent J Hyams (1924–98) in 1968 as Director of Otolaryngologic Pathology at the Armed Forces Institute of Pathology, Washington and in 1974 the publication of the textbook *Tumors of the Head and Neck* by John G Batsakis (1929–2013)[33, 34] were other landmark events in the development of head and neck pathology. The specialty of head and neck pathology has culminated in the publication, by the World Health Organization, of *A Classification of Head And Neck Tumours* ('The Blue Book'), the most recent edition of which was published in 2017.[35]

Radiology

Computerized tomography (CT) was invented and its early clinical application defined at the Atkinson Morley Hospital, London, England in 1971. The pioneering work of Sir Godfrey Hounsfield (1919–2004) in collaboration with Allan Cormack (1924–98), which underpinned the development of CT, led to both sharing the 1979 Nobel Prize for Physiology or Medicine. Subsequently, magnetic resonance imaging (MRI) was developed by Paul C Lauterbur (1829–2007) of Pittsburg and Peter Mansfield (1933–2017) of Nottingham. Their pioneering work culminated in them sharing the Nobel Prize for Physiology or Medicine in 2003. Continuing the progression of the development of ever more sensitive imaging modalities, in 1999, David Townsend, Ronald Nutt and colleagues in Pittsburg, developed positron emission tomography (PET/CT) for diagnostic use in clinical oncology.[8] This technique is now firmly established in the investigative work-up of patients with head and neck cancer, particularly in patients presenting with occult primary disease or in those where treatment failure is suspected.

Radiotherapy

In the 1920s, ionizing radiation, delivered as an external beam or by the placement of interstitial rods, was first used to treat patients with head and neck cancer. Henri Coutard (1876–1950) described his technique of protracted radiation therapy, which became so popular and accepted in many centres[36] that, for a time, surgery was partially displaced as a primary modality in the treatment of head and neck cancer. Hayes Martin, an admirer of Crile and a pioneer of head and neck surgery, although trained in the use of ionizing radiation, was vociferous in his resistance to the use of radiation for many cancers, primarily because of its toxicity profile and unpredictable ability to effect cure.[37] As outlined above, in these early days, the administration of radiotherapy was limited to orthovoltage generators and radium implants, resulting in a high degree of skin damage, poor cure rates and a myriad of attendant complications. By the 1950s the era of modern radiotherapy had begun with the advent of the linear accelerator and telecobalt units, which generated supervoltage radiation. Early advocates, such as Gilbert Fletcher (1911–92) in the United States,[38] and Manuel Ledermann (1912–84) in the UK,[39] strongly recommended external beam radiotherapy as the primary treatment modality for larynx cancer and cancers of other head and neck sites. The net effect of the work of these early advocates was that radiotherapy as a primary treatment for many head and neck cancers became popular and remains so, even today, in much of Northern Europe, the United States and Canada. The use of post-operative radiotherapy, following definitive surgical resection, became standard care during the 1970s. This combined management, which involved radiotherapy commencing after healing and within 6 weeks of surgery, was shown to definitively improve cure rates when compared with either surgery or radiotherapy alone or when salvage surgery was used after radiotherapy failure.[40] During the late 1980s advancements in computer software and imaging technology led to the development of three-dimensional (3D) image-guided targeting of radiation fields in an attempt to maximize tumour dose whilst minimizing radiation doses to adjacent normal tissues. The introduction of multileaf collimators facilitated an increase in the numbers of beams that could be delivered without a prolonged extension of the treatment time. The result was the emergence of 3D conformal radiotherapy, which allowed further refinement of radiation delivery to image-defined targets. Further improvements to radiation delivery precision occurred throughout the 1990s with the introduction of intensity-modulated radiation therapy (IMRT), which offers a higher degree of dose conformality

to maximize tumour dosing with greater sparing of normal tissue toxicity.[41]

Radiotherapy alone or in combination with cisplatin-based chemotherapy remains today a mainstay of treatment for many cancers of the head and neck in many centres throughout the world – particularly the developed world. Important studies which have led to this situation include the Department of Veterans Affairs (VA) Laryngeal Cancer Study, which, in 1991, demonstrated that response to chemotherapy was an excellent predictor to response to radiation therapy in cases of advanced laryngeal cancer.[42] Many high-quality randomized studies have also shown the utility of concomitant chemoradiotherapy in the management of head and neck cancers. The attraction of this approach is the avoidance of surgery and therefore, particularly for larynx cancer, the potential for preserving laryngeal function. This approach, however, is the subject of much ongoing debate as the treatment is toxic and difficult to tolerate by older patients with poorer performance status. Moreover, it has yet to be firmly established that preservation of the larynx amounts to the same as preservation of laryngeal *function* for the majority of patients treated this way.[43]

Surgery of the oral cavity

By the turn of the 19th century, it had become obvious to surgeons treating oral cavity cancer that treatment failure was most frequently associated with recurrent disease at the primary site and locally in the neck. This prompted surgeons to undertake more radical incisions of the primary tumour and to include removal of the cervical lymph nodes in an attempt to minimize the risk of locoregionally recurrent disease. Polya and von Navratil, in 1902, described the lymphatic drainage of the oral cavity, demonstrating that 50% of the lymphatics traversed the mandibular periosteum [published in German]. This resulted in the development of the concept of *en-bloc* resection and laid the foundations of the original composite (soft tissue and bone) resection for oral cancer. Almost concurrently, in 1906, the American surgeon and pioneer of neck dissection surgery, George Crile (1864–1943) described his approach to head and neck tumours, thus laying the foundation of the present-day approaches to neck dissection surgery.[44] Crile was an extremely creative surgeon, even developing pneumatic suits for patients to maintain their blood pressure during extensive surgical procedures. He also developed a carotid clamp that would reduce but not completely occlude carotid blood flow in an attempt to reduce the technical challenge of surgical bleeding as well as reducing blood loss. In Britain, the pioneering work in head and neck surgery of Henry Butlin (1845–1912) (considered to be the first head and neck surgeon), was continued by John Bland-Sutton (1855–1936) and later St. Clair Thompson (1859–1943) and Alexander Marsden (1832–1902), as well as Wilfred Lewis Trotter (1872–1939).[7] In spite of Crile's efforts to promote ever more radical surgery, the vogue for extensive procedures faded from the scene for a time, because of excessive mortality and apparent indifference in the surgical community.[13, 27]

Neck surgery

In 1927, George Harold Semken (1875–1946) who worked in the New York Skin and Cancer Hospital, excised *en bloc* (later called a composite operation) a primary mouth lesion that involved the corner of the mouth, buccal mucosa and lower jaw and the lymph nodes of the neck. In 1932, Grant E Ward (1896–1958), in Johns Hopkins, performed the first composite *en-bloc* resection, which consisted of a subtotal excision of the tongue, floor of mouth, and mandible in continuity with a radical neck dissection.[1, 45, 46] In 1951 Hayes Martin published a large series of 1450 cases of radical neck dissections, for involved lymph nodes as part of treatment for tumours emanating from all primary sites: so-called therapeutic neck dissection. He did not advocate surgery for the neck in the absence of obviously involved lymph nodes: so-called elective neck dissection.[47]

As an aside, a major innovation in the management of head and neck cancer at this point in time was the description in 1934, by Martin and Ellis, of fine-needle aspiration cytology (FNAC) as a diagnostic tool for enlarged cervical lymph nodes, a development that would dramatically alter the treatment of head and neck malignancy and thyroid disease over the next 75 years.[48]

Neck dissection surgery, the landmark publication by Hayes Martin in 1951,[47] suggested an extension of the surgery previously described by George Crile in 1906 to include resection of the spinal accessory nerve, even when not involved by tumour. In contrast, Crile had recommended preservation of the nerve when not involved by tumour.[46]

Surgical opinion differed about the need for elective neck dissection and those supportive of the approach considered that a radical neck dissection was 'too radical' and clinically unnecessary.[49, 50] This debate continues to this date about the radicality of surgery for tumour positive neck disease. Ettore Bocca (1914–2003) from Italy, popularized the modified neck dissection, where fascial compartment dissection of the cervical lymph nodes with preservation of the non-lymphatic structures (internal jugular vein, spinal accessory nerve and sternocleidomastoid muscle) was performed. Management of neck disease evolved throughout the 1960s and 1970s following the descriptions of selective neck dissection by Osvaldo Suarez (1914–1979) in South America and Ettore Bocca in Italy.[51–53] In 1990 Jatin Shah and colleagues evaluated the histological patterns of lymph node metastasis in patients undergoing elective and therapeutic radical neck dissection, in a series in which all patients underwent a radical neck dissection, irrespective of the primary pre-treatment nodal stage. Based on these data, which showed that the patterns of lymph node metastasis could be largely predicted, elective dissection of selective lymph node levels most at risk was proposed as an alternative to elective modified radical or radical neck dissection.[54]

In addition to the data that show metastatic spread in cervical lymph nodes could be predicted, the spread of tumour within a lymph node to broach the lymph node fibrous capsule – extracapsular spread (ECS) – was identified as an important negative prognostic factor even when

present in small apparently non-metastatic lymph nodes. ECS was identified in 20% of clinically negative necks in patients with supraglottic cancer who underwent elective neck dissection. This finding of ECS and multiple positive lymph nodes, by the Eugene Nicholas Myers (1933b) team from Pittsburgh, became indications for post-operative radiotherapy and currently chemotherapy is also suggested in the context of ECS.[55]

The trend towards modified radical and elective neck dissection was stimulated in an effort to avoid the not insignificant functional and cosmetic consequences of radical neck dissection. Data reported in the 1990s confirmed that selective neck dissection was as effective as modified neck dissection in patients with clinically positive lymph node disease.[56, 57] Identification and removal of the first echelon drainage lymph nodes, so-called sentinel lymph nodes, following the injection of isotope solution into or around the primary oral cancer, is increasingly used to determine whether neck dissection is needed at all.[57–59] It has been proposed and agreed by the International Head and Neck Scientific Group (IHNSG) that a logical nomenclature for the different types of neck dissections be recommended both for clinical and research purposes.[60] Consequently, the IHNSG has summarized the current philosophy in the surgical management for head and neck squamous cell carcinoma.[61]

Reconstructive surgery

The most important surgical innovations of the past 40–50 years have, however, been in the development of approaches to reconstruct ablative defects of the head and neck. In the 1960s, several surgical innovations helped reduce the morbidity of head and neck ablative surgery. In particular the increasing use of very reliable axial pattern flaps to reconstruct large oral cavity and neck defects resulted in decreased morbidity and a considerable shortening of post-operative hospital stay. Foremost among these were the descriptions of the forehead flap for oral reconstruction popularized by Ian McGregor (1921–98) and his wife Mary McGregor[62] and the deltopectoral flap described in the United States by Vahram Y Bakamjian (1918–2010) and colleagues. A H Martin Littlewood (1923–2004), who was a UK Fellow for six months at Roswell Park at the same time (1961), who returned to Warrington and practiced as a plastic surgeon.[63] In the late 1970s, the description of the pectoralis major myocutaneous flap by Stephan Ariyan[64] transformed head and neck oncologic surgery as patients could be offered a single-stage reliable reconstruction with minimal donor site morbidity. In addition, the ease of harvest and transfer of the pectoralis major flap made it a technique that any head and neck-trained surgeon could perform, broadening the scope of reconstructive surgery to other disciplines outside plastic surgery.

The late 1960s and early 1970s heralded the era of reconstructive microsurgery, which has since transformed the practice of contemporary head and neck surgery, to the enormous benefit of patients and healthcare providers. The concept of free-tissue transfer had been developed years earlier, but was limited by the quality and availability of microvascular sutures, appropriate instruments and operating magnification. Jacobsen and Suarez first described the repair of vessels under 2 mm diameter in 1960. The first free-tissue transfer of a composite (soft tissue and bone) flap was performed by G Ian Taylor and Rollin K Daniel in 1973.[65] Subsequent developments in reconstructive microsurgery have resulted in the description of a plethora of free flaps available for head and neck reconstruction championed by a number of extremely gifted reconstructive microsurgeons, including Kiyonori Harii, Harry J Buncke (1922–2008), Ralph T Manktelow, Mark Urken and many others.

Commonly used flaps in contemporary head and neck surgical practice include: the radial forearm flap described by GF Yang in 1983[66] and popularized for oral cavity and oromandibular reconstruction by David Soutar; the composite fibular flap, originally described by G Ian Taylor of Australia in 1977[67] and popularized by David Hidalgo and Alica Rekow for mandibular reconstruction in 1995;[68] and the anterolateral thigh flap described by YG Song et al in 1984[69] and popularized for head and neck reconstruction by Fu-chan Wei et al in 2002.[70] The ubiquitous application and the expansion of training in the use of microvascular free flap techniques has resulted in major changes in the specialty backgrounds of surgeons performing these techniques. Head and neck reconstruction is no longer the preserve of the plastic surgeon, with maxillofacial surgeons and even otolaryngologists/head and neck surgeons assuming pre-eminence in this field.[71, 72]

HEAD AND NECK SOCIETIES AND LEADERS

Hayes Martin (1892–1977) and Grant Ward (1896–1958) in 1952, and 50 selected American general surgeons were invited to serve as founding members of the Society of Head and Neck Surgeons, most were their former residents/students, and practiced in general or plastic surgery. Martin, the first president of SHNS, prioritized his training position for general surgeons, at the exclusion of otolaryngologists. In 1958, a group of otolaryngologists, John Conley (1912–99) the first president, George Sisson (1920–2006) and others conceived the American Society for Head and Neck Surgery, with a desire to foster participation with the American College of Surgeons.[73] Both organizations thrived in parallel for several decades, but as general surgeons waned in their enthusiasm and otolaryngologists became the dominant specialty in head and neck surgery, the two societies merged into the American Head and Neck Society (AHNS – www.ahns.org) in 1998.[74]

In Britain during the 1960s, a similar discussion was had as had been in the US, between a number of general surgeons about setting up a national head and neck society and linking such national societies with an International Association of Head and Neck Oncologists. In late 1967, a decision was taken to set up the Association of Head and Neck Oncologists of Great Britain (AHNOGB) with Mr. Ronald Raven (1904–1992), a London

general surgeon, as President, Professor Brian ED Cooke (1920–2007), an oral medicine and oral pathologist, from the University of Cardiff and Dr Manuel Lederman (1912–1984), a London radiotherapist, both as Vice-Presidents, Mr Douglas Ranger (1916–1997), a London ENT Surgeon as Honorary Secretary, and Mr Michael Harmer (1912–1998), a London general surgeon, as Honorary Treasurer. An additional nine members were invited to join the National Committee, and 78 letters of invitation were sent to doctors working in the field about the formation of a head and neck society. In January 1968, the inaugural meeting was held of the AHNOGB at the Royal Marsden Hospital.[75] In 1995, a decision was made to change the name of the organization to the British Association of Head and Neck Oncologists (BAHNO – www.bahno.org) to more reflect its broader clinician base, multidisciplinary working and membership of the society.

Unlike in many other countries, head and neck cancer surgical services are provided by otorhinolaryngology – head and neck surgery (ORL-HNS) and oral and maxillofacial surgery (OMFS) in an equitable fashion.[2] This resulted in the UK when NHS hospital consultant dentists (BDS) had to admit their patients overnight under the case of a named consultant medical clinician. To remedy that clinical situation, dentists who wished to pursue a career in head and neck surgery, which commenced in the mid-1970s, became doubly qualified both in dentistry and medicine.

It is appropriate that recognition be given to a number of our former UK head and neck surgeons / leaders:

Ian Alexander McGregor (1921–1998) a head and neck plastic and reconstructive surgeon at Cannisburn Hospital Glasgow, Scotland. He graduated from Glasgow Medical School 1944, MRCS and FRCS 1950, and FRCS Glasgow 1962. He studied with Dr. Herbert Conway, New York Hospital in 1955, and set up the West of Scotland Regional Plastic Unit 1959. He authored two major publications Fundamental Techniques of Plastic Surgery and their Surgical Application (1975) which ran for nine editions, and Cancer of the Face and Mouth (1986). He was former President of the Royal College of Physicians and Surgeons of Glasgow 1984–1986, and Presidents of the British Plastic Surgeons and the Association of Head and Neck Oncologists of Great Britain.

Sir Donald Harrison (1925–2003), a London Otolaryngologist, was the first UK Professor of ORL 1963. He published on the Anatomy and Physiology of the Mammalian Larynx, and Tumours of the Upper Jaw. He retired and was knighted in 1990;

Philip Stell (1934–2004), of Liverpool, and when appointed was the second UK Professor of ORL 1979. He did his fellowship with Joseph Ogura, St Louis, USA in 1956. He founded the ORS Society 1978, and the Journal Clinical Otolaryngology 1975. Stell couthored with Arnold Maran the first UK textbook on Head and Neck Surgery in 1972 which is now going into its 6th Edition. A prolific writer and linguist who was fluent in Dutch, German, French and Spanish, Stell translated 11 foreign medical textbooks into English. He retired from clinical practice in 1992 on grounds of ill health. He was awarded an MD on medieval history at York University and was recognized with a MBE by the Queen for his contribution to medieval history.

John Samuel Pattison (Iain) Wilson (1923–2006), a London plastic surgeon who worked at St Georges, Queen Mary's Roehampton, the Westminster and Royal Marsden; he was greatly liked as a teacher by his residents.

Henry Jagoe Shaw (1922–2007), a London Otolaryngologist, appointed surgon in 1962 at the Royal Marsden and St Mary's Hospitals, he did a fellowship with Hayes Martin in New York (1953–1954) and another year at Bellview Hospital, New York.

Barrie Thomas Evans (1946–2015), an Oral and Maxillofacial Surgeon at Southampton General Hospital, appointed in 1988. Developed a major head and neck, skull base surgical service before retiring in 2012 from the National Health Service.He was the first Chairman of the head and neck Interface Training Programme at the Royal College of Surgeons.

Omar Shaheen (1931–2016), an Otolaryngologist at Guy's Hospital, did his fellowship in Iowa, returning in 1963, specialized in thyroid disease, and trained a generation of young surgeons to follow his surgical principles and techniques which resulted in many of the current head and neck surgeons in the UK.

Arnold (Arnie) George Dominic Maran (1937–2017), an Edinburgh Otolaryngologist who when appointed was the third UK Professor of ORL in 1988, he did his fellowship with Brian McCabe, Iowa (1966–1967) before returning to Scotland, and was ultimately appointed at the Edinburgh Royal Infirmary in 1975. Not only was he an expert on head and neck cancer but set up the first voice centre in the late 1980s for which he became dubbed 'the voice doctor'. He was a frequent co-author with his colleague Professor P M Stell in the 1970s including the textbook *Head and Neck Surgery* in 1972. He authored several textbooks on ORL and travelled widely acquiring many accolades. He was elected President of the Royal College of Surgeon of Edinburgh from 1997 to 2000. He was a musician and jazz enthusiast, as well as a golfer – all resulting in publishing books in his retirement, including one on the Sicilian Mafia influenced by his heritage and an incident involving his great uncle.

The European Head and Neck Society (EHNS – www.ehns.org) was formally established in 2006 in Brussels by the signing of the official documents by the founding Board: Jean Louis Lefebvre (France), Rene Leemans (Holland), Jan Olofsson (Norway), Dominique Chevalier (France), Guy Andre (Belgium) and Patrick Bradley (UK). Over several decades the Dutch, British and Scandinavian head and neck societies had met frequently and these gatherings were considered of benefit to all who attended. A decision was made to hold a European Head and Neck

Meeting in Lille, France in 2001, followed by a second meeting in 2003; these suceessful meetings led to a consensus decision to create the European Head and Neck Society. The EHNS is composed of individual persons, national and multi-national societies, and associated study groups oriented towards head and neck cancer research, training and treatment throughout Europe.[74]

The International Federation of Head and Neck Oncologic Societies (IFHNOS – www.ifhnos.org) was established by Dr. Jatin Shah, New York who formed a steering committee at a meeting in London 1987 with representatives of 16 Head and Neck Organizations from around the World.[5] A constitution and bylaws were formulated and Jatin Shah was elected Secretary General. IFHNOS is a global organization established through cooperation of national and regional Societies and Organizations in the Specialty of Head and Neck Surgery and Oncology with membership from national and regional multidisciplinary organizations, representing 65 countries. The purpose of the Federation is to provide a common platform for Specialists in the field of Head and Neck Cancer to interact in professional matters of mutual interest. The Federation has grown with a membership of 43 Head and Neck Oncologic organizations, representing 65 countries. The Federation is able to reach over 5000 specialists. Quadrennial World congresses of the Federation have been held since 1998.

HEAD AND NECK SURGICAL TECHNIQUES

Surgery of the oropharynx

OPEN APPROACH

Over recent decades in the developed world, management of squamous cell carcinoma of the oropharynx, whether human papilloma virus (HPV) associated or not, has become dominated by non-surgical modalities, namely, radiotherapy +/– concurrent cisplatin-based chemotherapy. As a consequence, the surgical management of tumours of the oropharynx involving open access procedures including mandibular osteotomies or lingual release techniques has fallen into abeyance. That said, there are cases where the approach is still used – for example, in patients with advanced stage but still operable disease, who are unfit or too old for primary chemoradiotherapy. In these cases reconstruction of the ablative defect is almost always essential and techniques involving free-flap reconstructive surgery predominate.

TRANSORAL APPROACH

Transoral *en bloc* resection for tonsil tumours was initially described in 1951 by Pierre Charles Huet (1896–1947), a surgeon based in Paris.[77] Current transoral approaches for tonsil cancers in patients with early stage primary disease include transoral laser surgery (TOLS) and transoral robotic surgery (TORS) with integrated neck dissection and risk stratified radiation therapy, pioneered by Heinrich H Rudert, Wolfgang Steiner and Petra Ambrosch (Germany) and Gregory Weinstein (USA), respectively. Such approaches avoid the overall early- and long-term toxicity burden of non-surgical treatments, the morbidity associated with open approaches and free-flap reconstruction, whilst potentially conferring equitable oncological outcomes with better functional outcomes.

Surgery of the larynx

OPEN APPROACH

In 1913, Themistocles Gluck (1853–1942) and Johannes Sorensen (1862–1939) described improved approaches to the creation of the tracheostoma and repair of the pharynx after laryngectomy and arguably became the foundation of modern laryngopharyngeal ablative and reconstructive surgery.[78] It was not until the late 1950s that partial laryngeal surgery was considered an option to treat early stage cancer. The anatomy of the larynx had been studied by Joel Pressman (1901–68) of UCLA and John Kirchner (1915–2011) of Yale, who recognized compartmentalization of the glottis and supraglottis by fibrous bands and ligaments.[79–81] Many partial laryngeal resection procedures have been described over time, providing a wide range of choices of conservation surgical treatments, retaining the goal to cure while preserving laryngeal function in terms of voice and non-tracheostomized breathing. Jean Leroux-Robert described a frontolateral partial laryngectomy for unilateral vocal cord carcinomas, with minimal extension to the opposite side.[82] In 1951, Justo M Alonso (1886–1974) from Uruguay, one of the pioneers of partial laryngeal surgery, described techniques of vertical laryngectomy and horizontal supraglottic laryngectomy.[83] Many variations of this procedure have been described and are all encompassed within the term hemilaryngectomy.

The development of supraglottic laryngectomy was an extension of technique of pharyngectomy (superior and inferior), as described by Wilfred Trotter (1872–1939) in 1920; this resulted in Joseph Ogura (1915–83),[84] Max Som (1904–1990)[86] and Ettore Bocca[81] modifying the technique of supraglottic laryngectomy to that understood by the term today. In the late 1950s a more radical excision of more extensive glottic and supraglottic cancers was reported using a technique of supracricoid partial laryngectomy by Eduard Herbert Majer (1909–1991) and Walter Rieder (1921–1992), surgeons in Vienna, which became popular in Europe.[87] Olivier Laccourreye et al[88] popularized the procedure in the late 20th century in Europe, and Gregory Weinstein from Philadelphia[89] in the United States. A large series of 297 patients from the Institute Gustave-Roussy treated by subtotal laryngectomy between the years 1974 and 1997, reported 3- and 5-year overall survival rates of 92% and 88% respectively.[90] Italian surgeons continued to expand the indications laryngeal sparing surgery, building on the teachings of Italo Serafini (1936–2010) from Vittorio Veneto, who classified open partial horizontal laryngectomy, into three types: supraglottic laryngectomy (Type I); supracricoid

laryngectomy (Type II); and supratracheal laryngectomy (Type III), Type III being indicated for intermediate-to-advanced laryngeal cancers with subglottic extension.[91]

TRANSORAL APPROACH

Francis E 'Duke' Le Jeune Sr. (1894–1977) from New Orleans is credited as a pioneer of the modern era of endoscopic micro dissection of vocal cord cancer, but he had continued the work of Robert Clyde Lynch (1880–1931). The technique of micro laryngeal examination had been first reported by Gustav Killian (1860–1921) from Germany in 1910. Following the publication of the experience of Le Jeune, Charles Vaughan (1926–2014) and colleagues from the United States.[92] Following on from Lejeune, Charles Vaughan (1926–2014) and colleagues from the United States, and Oskar Kleinsasser (1929–2001) from Germany progressed and popularized the developments in minimally invasive surgery of the larynx,[93, 94] initial techniques that have been expanded and popularized by others. For example, M Stuart Strong and Geza J Jako (1930–2015) from Boston are credited with introducing the CO_2 laser for microsurgery of the larynx in the early 1970s;[95] Heinrich Rudert, Wolfgang Steiner and Petra Ambrosch from Germany,[96] published their systematic approach to the endoscopic transoral laser microsurgery (TLM) of laryngeal tumours fundamentally altered the landscape of the management approach for laryngeal malignancy. The introduction of transoral robotic surgery (TORS) in 2007 has further expanded the capabilities of endoscopic surgery.[97] The European Laryngological Society working committee, in an attempt to standardize the reporting of endolaryngeal surgical resection in the clinical and research setting, developed a classification based on the extent of glottic and supraglottic transoral endoscopic resection.[98, 99]

Surgery of the hypopharynx

OPEN APPROACH

Surgery for hypopharyngeal cancer was changed in the 1920s by Wilfred Louis Trotter (1872–1939) from London, and revived in the 1940s by Harold William Wookey (1889–1980) who worked in Toronto. Trotter described a lateral pharyngotomy to gain access, and using local cervical skin flaps to repair the defect, Wookey described the repair of a circumferential defect using a two-layered skin tube to create a neopharynx.[98, 99] who described a lateral pharyngotomy to gain access to the pharynx using local cervical skin flaps to repair the defect, thus avoiding the previously used more extensive pharyngolaryngectomy.[100, 101] As for pharyngolaryngectomy, the transcervical approaches to the hypopharynx may be classified into partial pharyngectomy with partial laryngectomy, total laryngectomy with partial pharyngectomy or circumferential laryngopharyngectomy with or without oesophagectomy.[102] The techniques used for repair of the pharyngeal defect (partial or total) progressed through all of the phases of development of flap reconstruction methods: local skin, pedicle skin, axial myocutaneous and viscus (stomach and colon), free soft tissue +/– bone and free viscus (gastro-omental flap), over a period of 60 years.[103]

TRANSORAL APPROACH

As with larynx cancer surgery, although function-sparing non-surgical treatment is considered standard of care in many centres in the developed world, TLM or TORS has been proposed for the management of hypopharynx cancer with the same aim of reducing the extent of surgery as well as the burden of post-treatment morbidity.[96, 104] The selection of appropriate treatment is of crucial importance in the achievement of optimal functional results and likely survival for these patients.[105]

Surgery of the paranasal sinuses and nasopharynx

OPEN APPROACH

The open approach using the lateral rhinotomy and the Weber-Ferguson transfacial incisions to access tumours of the ethmoid and maxillary sinus was not introduced until the 1970s. In 1963, Alfred Ketcham (1924–2017) first reported a series of patients who had undergone a combined craniofacial approach to anterior skull base malignancies.[106] Other surgeons have since continued and expanded on the trans cranial +/– endoscopic approaches. Noteworthy examples include Victor Schramm, Paul Donald and Dennis Kraus from the USA, Anthony Cheesman from the UK, William Wei from Hong Kong and Sultan Pradham from India. Developments have led to a reduction in post-operative complications and improved survival. As a consequence of the heterogeneous nature of tumours which may occur in this region, histology plays a great role in prognostication. Moreover, tumour extension, particularly intracranial extension, whether dura and/or brain, involvement and positive surgical resection margins all impact negatively on outcome.[107] As an extension of earlier techniques, William Wei from Hong Kong described the anterior-lateral maxillary swing approach in 1998, and reported his long-term results of 246 patients. During surgery, frozen section was used and clear margins were achieved in 78% of cases resulting in a 5-year local control rate of 75%. These were selected patients, however, and did not include patients with erosion at the skull base or invasion of the carotid artery.[108]

TRANSNASAL APPROACH

In the early 1980s, Erik Wigand (b.1931), Wolfgang Draf (1940–2012) and Walter Messerklinger (b.1920) as well as Heinz Stammberger (b.1946)[109] and colleagues from Graz, Austria introduced the concept of functional endoscopic sinus surgery (FESS), thereby providing the technical foundation for the development of minimally invasive nasal surgery. A number of groups around the world, most notably Amin Kassam, Ricard Carrau and Carl Snyderman[110] from the USA, Valerie Lund and Nicholas Spencer Jones from the UK and Giulio Cantu,

Pierro Nicolai and Paolo Casteinuovo from Italy, have extended these concepts and techniques, developing transnasal approaches to the management of anterior skull-base tumours. Endoscopic nasopharyngectomy has been reported to show promising short-term outcomes for early-stage recurrences of nasopharyngeal carcinoma but long-term follow-up is necessary to confirm effectiveness.[111] It is suggested that improvements in technology, robotic-assisted transnasal approaches, and improved suturing techniques and closure devices, will help decrease the rate of CSF leaks and lead to better patient outcomes.[112]

SURGERY OF THE TEMPORAL BONE MALIGNANCIES

Primary temporal bone malignancies are exceedingly rare, squamous cell carcinoma being the most common and are generally the focus of most publications. In a review of 100 temporal bone resections in 1975,[113] John S Lewis (1920–2005) from the Memorial Hospital, New York, published data on 80 patients with these tumours. The death rate reduced from 10% in 1954 to 5% in recent years. The overall 5-year cure rate was 25% for squamous cell carcinoma. Prior to this publication, primary temporal bone cancer was considered incurable, and was treated by radiotherapy alone. Currently, with improvements in disease staging by imaging techniques, surgery remains the primary treatment of temporal bone malignancy, with the use of radiotherapy as an adjuvant to surgery.[114, 115]

HEAD AND NECK SURGERY: THE PRESENT

With great foresight, Hayes Martin, on appointment as Chief of the Head and Neck Service in 1934, set up a weekly head and neck tumour board (multidisciplinary clinic). During the 20th century, this concept was introduced more widely and whilst it was adopted with varying enthusiasm initially, a multidisciplinary team (MDT) approach is now accepted as the 'gold standard' environment within which to manage patients with head and neck cancer (See Chapter 32, Multidisciplinary team working).[116, 117] Case presentations at an MDT, when all things are considered, may affect the treatment offered and will certainly standardize treatment approaches and improve standards of care to the benefit of patients.[118] The problems associated with the occasional head and neck surgeon ('the dabbler') on the treatment outcome was most forcefully highlighted by John ('Jack') J Lore (1923–2004) in a publication of 1987, when he advocated the need for added qualifications and training for future head and neck surgeons, as well as accreditation of the hospital ('dabblice') as being a suitable environment to perform such surgery, and referred to the market place as 'dabbloge'.[119] While the USA, Canada, some European nations (Finland, Netherlands and UK) and Brazil have developed structured additional education and training in head and neck oncology, awarding a 'Certificate of Completion of Fellowship', others have informal training programmes (Italy, Germany and Spain). The concept of such specialist training for future head and neck surgeons has not been universally embraced. Moreover, when instituted, the training programmes need formal assessment of competence on completion of training, overseen by an accrediting body.[120] The modern head and neck surgeon may specialize in a number of parent surgical disciplines including general surgery, plastic and reconstructive surgery, otolaryngology/head and neck surgery, oral and maxillofacial surgery, neurosurgery or endocrine surgery. This confirms the necessity for contemporary head and neck surgeons to assimilate broad but complementary surgical skillsets in order to optimally undertake the complex management of patients presenting with cancers of the head and neck region.

From the early 21st century the training of head and neck surgeons relied on the sheer volume of clinical exposure, rather than specifically designed curricula. In addition, it is recognized that there is a critical mass required to assimilate the necessary expertise to become a competent surgeon, hence the creation of tertiary surgical centres. As in many other surgical specialties and in keeping with the history of surgery, surgical advances are dependent upon advances in technology – and this is increasingly the case in the modern era. Recent developments have resulted on more emphasis being placed on minimally invasive strategies with the aim of maximizing cure whilst minimizing treatment-related short- and long-term side effects. This dynamic environment dictates that surgical training needs to maintain flexibility and relevance.[121–123] Future head and neck surgeons will be trained to work within specialist oncology teams that treat subsites of the head and neck: skull-base surgery, endocrine surgery, endoscopic surgery, laryngology and voice surgery, as well as reconstructive surgery. Additionally, there may be a future need for a head and neck rehabilitation specialist to optimally manage patients coping with adverse effects of treatment.

The era of expanding non-surgical treatment options and precision medicine, and difficulties in recruitment and retention of head and neck surgical trainees has led to commentaries such as 'Has head and neck surgery a real future?'[124] and 'Head and neck surgery in crisis',[125] raising questions about the future of head and neck surgery as a specialty. The modern head and neck surgeon should consider his or her role as a leader and coordinator of the MDT, consider him- or herself as an oncologist, and become an educator, researcher and incorporator of technological advances.[126] The future head and neck surgeon will remain an essential member of the head and neck MDT and accordingly, a stylized job description pertinent for the future head and neck surgeon has been proposed.[127] It is essential that all members of the MDT head and neck cancer team embrace and participate in ongoing research into personalized medicine and targeted therapies, where genomic characterization of tumour tissue or blood is anticipated to play an increasing role in how cancer treatment is selected and individualized.[128]

HEAD AND NECK SURGERY: THE FUTURE

Head and neck surgeons, for the foreseeable future, can rest assured that there will always be a need for their services in the diagnosis and management of patients with cancer of the head and neck. While the indications and selection of treatments fluctuate with time, the success of any cancer treatment is captured by the adage, 'first treatment is always best'. Presently patients with locally advanced disease, (T3 and T4, >N2), of the larynx and hypopharynx, and oropharynx, are treated primarily with chemoradiotherapy. This function-sparing approach has resulted in enhanced organ retention but there is a poor evidence-base to confirm that the retained organ's function in a meaningful way to the extent that overall quality of life is truly enhanced in patients treated this way.

Oral cavity cancers remain best treated by primary surgery, as are other head and neck malignant tumours such as thyroid and salivary glands, skin and temporal bone cancers. The salvage of the failure of organ preservation approaches and for patients treated by minimal invasive surgical strategies represents a difficult challenge for the head and neck surgical oncologist, particularly the selection of patients for whom further treatment will be curative or life enhancing.

Early stage cancers of the larynx and hypopharynx are also best treated surgically with no need for adjuvant treatments.

What is also essential, and which might not have been the case in days gone by, is the need for surgeons to understand the biology of the disease they are treating, to fully appreciate the advantages and limitations of the non-surgical treatments offered to patients, to quality assess and quality control surgical outcomes and validated surgical approaches as part of high-quality, optimally designed and powered randomized clinical trials. Only then will they be able to contribute fully within the multidisciplinary environment to the future management of patients presenting with head and neck cancer.

KEY POINTS

- The term Head and Neck Surgery was reintroduced to surgical specialties in the middle of the 20th century by Hayes Martin and Grant Ward, both general surgeons.
- Oral cancer was described in the 17th century and surgeons mainly concentrated on the removal of mouth and neck tumours. Laryngeal cancer was made more manageable with the introduction of cocaine in the 19th century. The use of radiation therapy was discovered in the late 19th century and was introduced in a formalized therapeutic manner for larynx cancer in the early quarter of the 20th century.
- Early head and neck surgeons were brave, courageous, fearless and speedy in the era before anaesthetic, blood transfusion, and antibiotics.
- Resulting from World Wars, reconstructive procedures were rekindled and rapid progress was made shifting from split skin to axial and regional flaps. The advent of revascularized free transfer of tissue in the late 20th Century, which including muscle and bone, further advanced the surgeon's ability to resect and reconstruct more major and more repair complex defects.
- In the US the Society of Head and Neck Surgeon was established in 1954 by a group of general surgeons, because of an exclusion law, the otolaryngologists formed The American Society for Head and Neck Surgeons in 1956. In 1998, both societies amalgamated into The American Head and Neck Society and agreed a structured training programme for future head and neck surgeons. Similar events have been repeated in other countries.
- While progress was being achieved by performing more major resection on more advanced stage disease and being able to reconstruct the defect, a common event was that the tumour recurred locally, evidence was shown that post-operative radiotherapy reduced such an event happening.
- With advances in diagnostic imaging and anaesthesia it became possible for surgeons to change the extent of surgery from the traditional 'open approach' to a 'closed approach' using endoscopic telescope equipment under radiological monitoring and allowed surgical access to several 'hidden corners', such as the skull-base, parapharynx and temporal bone, inventing the term 'minimally invasive surgery'.
- The introduction of the surgical robot has proven to be an effective technique to safely treat most tumours of the head and neck irrespective of site or access. So far the evidence shows that the functional and cosmetic results are equal if not improved when compared with the standard open surgical approach. The comparison with non-surgical treatment may be difficult due to the inherent selection bias of favourable patients and tumour selected.
- There will always be a role for surgery in the diagnosis and management of head and neck tumours but the role may change over time. It is therefore important that future surgeons be educated as surgeon oncologists and play a major role in the decision-making process for treatment of patients. In time in the developed world at present centralization of head and neck cancer treatment will continue to be advocated and funded to optimize patient survival and minimize morbidity. It is paramount that this role is practiced and enforced within the multi-professional and multidisciplinary clinical group.

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CHAPTER 2

AETIOLOGY OF HEAD AND NECK CANCER

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SEARCH STRATEGY

Data in this chapter may be updated by a PubMed search using the keywords: head and neck cancer aetiology and head and neck cancer causes.

INTRODUCTION

Squamous cell cancer constitutes the most common head and neck malignancy and is related to tobacco and/or alcohol usage. Non-squamous malignancy includes thyroid cancer, salivary gland cancer and sarcomas. These malignancies are not associated with tobacco and/or alcohol usage.

According to the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) programmes of the United States, between 1975 and 2010 the incidence for most head and neck cancers sites has globally decreased except for tongue, tonsil, salivary glands and thyroid.[1] Estimated new head and neck cancer cases and deaths for 2013 are shown in **Table 2.1**.[2] A decreased incidence of oral cavity cancer has been reported in the last 15 years, widely attributed to a reduction in tobacco use.[3] In contrast, the incidence of oropharyngeal cancer has risen in recent years, a phenomenon that has been linked mainly to the emergence of human papillomavirus (HPV) infection.[4] A more comprehensive treatment of epidemiology of head and neck cancers is discussed in Chapter 3, Epidemiology of head and neck cancer.

SQUAMOUS MALIGNANT TUMOURS

Squamous cell carcinoma of the head and neck encompasses cancer of the oral cavity, oropharynx, larynx and hypopharynx, nasopharynx, nasal cavity and paranasal sinuses. The two most important factors in the aetiology of head and neck cancer are tobacco and alcohol.[5] There is a synergistic interaction between these two agents that is multiplicative for the mouth, additive for larynx and between additive and multiplicative for oesophagus.[6]

TABLE 2.1 Estimated new cancer cases and deaths in United States, 2013

	Estimated cases			Estimated deaths		
	Both sexes	Male	Female	Both sexes	Male	Female
Oral cavity/oropharynx	41 380	29 620	11 760	7890	5500	2390
Tongue	13 590	9900	3690	2070	1380	690
Mouth	11 400	6730	4670	1800	1080	720
Other oral cavity	2460	1790	670	1640	1260	380
Oropharynx	13 930	11 200	2730	2400	1790	610
Larynx	12 260	9680	2580	3630	2860	770
Thyroid	60 220	14 910	45 310	1850	810	1040

A large case-control study from the United States shows good evidence of a dose-response relationship for both tobacco and alcohol.[7, 8] Other factors are also implicated in the aetiology of squamous cell head and neck cancer such as diet, viruses, occupational agents, pollutants and genetic influences, but few case-controlled epidemiological studies have been carried out.

Since the histological distribution and aetiopathological considerations for cancers at various sites within the head and neck are distinct, these tumours will be discussed in more detail under separate anatomic sites.

Cancer of the oral cavity

The main aetiological factors for oral cavity cancer are smoking and alcohol.[7, 8] It is estimated that in 2013 there will be 27 450 new cases of oral cavity cancer in the United States, 14 420 male and 9030 female.[2] In the UK it is the 15th most common cancer among men, and 16th among women.[9] The incidence and mortality increase with age with over 85% cases occurring after the 5th decade. Over the last 30 years there has been a slight increase in oral cancer mainly attributable to the increase in tongue cancer in young women.[10–12] A detailed treatment of the global epidemiology is found elsewhere in the text.

TOBACCO

Tobacco consumption

Tobacco is the most important factor and over 90% of patients have a history of smoking. Tobacco contains over 30 known carcinogens such as polycyclic aromatic hydrocarbons and nitrosamines.[13] There is a synergistic interaction with alcohol due to the increased mucosal absorption of these carcinogens due to increased solubility of the carcinogens in alcohol compared with aqueous saliva. The use of filtered cigarettes reduces this exposure and stopping smoking reduces the risk of head and neck cancer.[14] The risk of oral cancer is reduced by 30% in those who have discontinued for 1–9 years and by 50% for those who have discontinued for more than 9 years,[15] but it is unlikely that it ever returns to the baseline as compared to the rest of the population.[16] Pipe and cigar smokers have an increased risk of oral cancer compared to other head and neck subsites.[17] This is thought to be due to the type of tobacco used. Several reports have shown a progressive decline in tobacco consumption over the last 25 years.[18] It is possible that the decrease in tobacco use accounts for the decrease in oral cancer incidence. Also, a decrease of the prevalence of tobacco use has been reported among oral cancer patients. A recent descriptive report of the prevalence of tobacco use among oral cancer patients has shown a significant decrease of smoking in oral cancer patients.[19] This could suggest that other etiological factors could be responsible for part of patients with oral cancer. Further studies on the aetiology of oral cancer in non-smoking patients are warranted.

Smokeless tobacco

Oral cancer is strongly associated with different forms of smokeless tobacco consumed by chewing. These include Bidi, Chutta, Paan, Khaini and Toombak. This is particularly common in the Indian subcontinent and accounts for the high incidence of oral cancer in these countries. Oral cancer increases in a dose dependent fashion with these agents.[20, 21] There is also a strong association between the subsite of oral cancer and the site where the tobacco is placed. In India and parts of Asia, oral tobacco is mixed with betel leaf, slated lime and areca nut to form a quid called 'paan'. The lime lowers the pH, which accelerates the release of alkaloids from both the tobacco and areca nut. Chewing paan correlates with alveolobuccal cancer.[22] Paan is also strongly associated with a premalignant lesion oral submucous fibrosis.[23] Bidi smoking causes cancer of the oral commissure, oral tongue and also base of tongue. Chutta is associated with cancer of the hard palate and palatine arch in India.[24] Khaini, a mixture of tobacco and lime that is retained in the inferior gingivobuccal sulcus, leads to cancer in this site.[25]

Marijuana

When marijuana is smoked, a wide range of potential carcinogens are released and absorbed including polycyclic aromatic hydrocarbons, benzopyrene, phenols, phytosterols, acids and terpenes.[26, 27] A study from Memorial Sloan Kettering Cancer Center reported an overall risk of 2.6 compared to non-users.[28]

ALCOHOL

Alcohol is believed to act in a synergistic fashion with tobacco.[7, 29, 30] However, some case control and cohort studies have shown an increased risk of cancer even in non-smokers.[31] The precise mechanism by which alcohol causes cancer is not clearly defined as alcohol itself is not a carcinogen. Possible mechanisms include:

- Alcohol may act as a solvent increasing the cellular permeability of tobacco carcinogens through the mucosa of the upper aerodigestive tract.[29]
- The non-alcohol constituents of various alcoholic beverages may have carcinogenic activities.
- The immediate metabolite of ethanol is acetaldehyde and this may have a locally damaging effect on cells.[32]
- Chronic alcohol use may upregulate enzymes of the cytochrome p450 system, which may result in the activation of procarcinogens into carcinogens.
- Alcohol can also decrease the activity of DNA repair enzymes resulting in increased chromosomal damage.
- Alcohol impairs immunity due to a reduction in T cell number, decreased mitogenic activity and macrophage activity.
- Alcohol is high in calories, which suppresses appetite in heavy drinkers. Metabolism is further damaged by liver disease resulting in nutritional deficiencies and therefore lowered resistance to cancer.

DENTAL FACTORS

Poor oral hygiene is associated with oral cancer. This may be due to chronic inflammation of the gingiva.[33]

Alternatively, it may be due to an alteration in the oral microbiome.[34, 35] Painful or loose fitting dentures have also been associated with oral and oropharyngeal cancer.[36] This may also be due to chronic inflammation. There is some evidence suggesting mouthwashes containing alcohol may also be important.[37]

INFECTIONS

In oral cancer, several viruses have been implicated in carcinogenesis including human papilloma virus (HPV), human immunodeficiency virus (HIV) and herpes simplex virus (HSV).

Human papillomavirus

For oral cancer, the pathogenetic relationship with HPV is unclear. Some authors have dismissed a link between oral cavity cancer and HPV infection, based on the very low prevalence rates reported in some studies.[38–40] For instance, in the International Agency for Research on Cancer multicentre study, HPV DNA was detected in biopsy specimens in only 3.9% of 766 cancers of the oral cavity with valid PCR results.[38] In contrast, other authors have reported that the infection of oral cavity cells by HPV is not a rare phenomenon. Analysis of reports focused only on oral cavity cancer have reported a prevalence as high as oropharynx, around 60% or 70%,[41, 42] even in subsites not common for this infection (such as gums or floor of mouth). Therefore, the relationship between oral cavity cancer and HPV infection is not a closed case, and further research is necessary to elucidate its role.

Human immunodeficiency virus

A recent study from New York showed HIV infection in 5% of head and neck cancer patients.[43] In patients under 45, HIV infection was present in over 20%. Due to the depressed immunity in HIV patients, the head and neck cancers observed were more advanced in the HIV group. In addition, HIV infection is more common in inner city populations and certain socioeconomic groups and this will also contribute to the advanced stage at presentation of these patients.[44]

Herpes simplex virus

Several studies have shown that patients with oral cancer have higher antibodies to HSV, but this does not prove a causal relationship.[45] Antibody levels are higher in smokers and even higher in smokers with oral cancer. It is possible that the immunosuppression produced by smoking may lead to a HSV chronic carrier state resulting in raised antibody levels. HSV-type protein has been reported in 42% of patients with oral cancer and 0% in control patients.[46] However, there is little evidence that HSV gene sequences are present in oral cancer cells or any evidence of gene integration. Therefore, there is currently little emphasis on HSV in head and neck cancer.

NUTRITIONAL FACTORS

Several studies suggest high fruit and vegetable intake is associated with a decreased risk of head and neck cancer. This may be due to increased intake of the antioxidants or free radical scavenging vitamins A, C and E.[47–49] La Vecchia et al, estimated that up to 15% of oral and pharyngeal cancers in Europe can be attributed to dietary deficiencies.[50] Some studies have shown an increased risk with red meat intake and salted meat.[51, 52]

GENETIC AND IMMUNOLOGIC PREDISPOSITION

Although smoking is the main risk factor, not all people who smoke develop head and neck cancer. Therefore, genetic and immunologic factors also play a role. There are several genetic conditions that are associated with increased risk. Li-Fraumeni syndrome, an autosomal dominant condition involving mutation of the *p53* gene, has been associated with head and neck cancer in patients with minimal tobacco exposure.[53, 54] Fanconi's anaemia, Bloom syndrome and ataxia-telangiectasia are autosomal recessive disorders associated with increased chromosomal fragility and cancer susceptibility. There is an increased incidence of head and neck cancer in each of these conditions.[55–58] There is a genetic susceptibility in the capacity to metabolize carcinogens and repair consequent DNA damage. This involves polymorphisms in GST genes,[59–61] CYP genes,[62, 63] and the cytochrome *p450* system.[64]

Immunologic factors are also important. Patients treated for bone marrow transplants and organ transplants have an increased incidence of skin cancer and oral cavity cancer. This may be due to the long-term use of immunosuppressive drugs.[65, 66]

Cancer of the oropharynx

Recent studies have shown a dramatic change in the aetiology of oropharyngeal cancer from a cancer caused by smoking and alcohol to a cancer now predominantly caused by HPV.[3] Cancer of the oropharynx is the third most common head and neck cancer after larynx and oral cavity. It is estimated that in 2013 there will be 13 930 new cases of oropharynx cancer in the United States, 11 200 male and 2730 female.[2] In the UK, it has an increasing incidence, reported in near 6% annual percentage change, especially among men.[67, 68] Raised incidence rates are observed in Netherlands, India, France and Italy.[69–71] This increase in tonsil and base of tongue cancer over the last decade is largely due to HPV infection of the palatine and lingual tonsils, and has been called an epidemic of HPV-associated oropharyngeal cancer.[72, 73]

HPV has been extensively studied and there seems to be a definite association between virus and tumour formation.[72, 74] The proportion of cancers with HPV varies with site with a strong association with tonsil cancer.[75,76] Steinberg and DiLorenzo reported HPV infection to be highest in tonsil (74%), followed by larynx (30%), tongue (22%), nasopharynx (21%) and floor of mouth (5%).[77] HPV exists in many different serotypes and specific serotypes are associated with head and neck cancer. For example,

benign lesions such as the common wart are associated with 'low-risk types' and include HPV 6, 11, 13, 32.[78] High-risk types are associated with premalignant lesions and squamous cell carcinoma and include HPVs 16, 18, 31, 33, 35, 39.[78, 79] HPV 16 and 18 appear to be the most common types associated with squamous cell carcinoma. HPV 31, 33 and 35 are more commonly associated with cervical cancer and are not found in oropharyngeal cancer.[80, 81] The E6 and E7 open reading frames (ORFs) of the high risk HPVs are particularly important. They bind to and inactivate tumour suppressor genes *p53* and *pRb* respectively.[82] This allows uncontrolled cell proliferation, which can result in genomic instability and cellular transformation.[83] There is no relationship between clinical stage and HPV status in squamous cell carcinoma of the head and neck. This suggests HPV infection is not a late event in the evolution of head and neck cancer. As mentioned above, the highest incidence of HPV is found in tonsil cancer suggesting that there is a predilection of HPV infection for patients with tonsillar carcinoma.[75, 76] Patients with HPV positive tonsil cancer tend to be young, non-smokers and non-drinkers. The molecular characteristics are completely different to HPV negative tonsil cancers where *p53* is often mutated due to carcinogens in tobacco smoke and amplification of cyclin D1. HPV-positive cancers often have abnormalities in the PIK3/AkT/mTOR pathway resulting in activation of this pathway.[84, 85] Probably due to the different pathogenetic origin, HPV-positive tonsil cancers have shown a better prognosis.[86]

Cancer of the larynx and hypopharynx

The American Cancer Society estimates that 12 260 new cases of laryngeal cancer (9680 in men and 2580 in women) will be diagnosed, and 3630 people (2860 men and 770 women) will die from the disease in the United States in 2013.[2] These numbers are falling by around 2% to 3% a year, mainly because fewer people are smoking.[1, 3] About 60% of larynx cancers start in the glottis, 35% develop in the supraglottic region and the remaining 5% occur in the subglottis.[87]

Cancer of the hypopharynx accounts for 10% of all squamous cell cancers of the upper aerodigestive tract.[87] In the UK, the overall incidence is 1 per 100 000 per annum. There is a high incidence in northern France of 14.8 per 100 000.[88, 89] Subsites of the hypopharynx include pyriform fossa (70%), postcricoid area (15%) and posterior pharyngeal wall (15%).[87] The pyriform fossa is the commonest subsite in North America and France. Postcricoid lesions appear more commonly in Northern Europe. The mean age at presentation is 60 years. Pyriform fossa and post pharyngeal wall have a male predominance of 5 to 20 : 1 in North America[90, 91] with 50 : 1 in France.[92] Postcricoid lesions show a female preponderance 1.5 : 1.[93–95]

TOBACCO AND ALCOHOL

There is a strong association between laryngeal cancer and cigarette smoking. The relative risk of laryngeal cancer between smokers and non-smokers is 15.5 in men and 12.4 in women.[96] Environmental tobacco smoke also increases the risk of laryngeal cancer.[97] The combined use of tobacco and alcohol increases the risk of laryngeal cancer by 50% over the estimated risk if these factors were considered additive.[98–100] Risk is greater for hypopharyngeal cancer than laryngeal cancer.[101] This variation in the risk of alcohol is shown for different sites in the larynx (i.e. supraglottic cancer patients are more likely than glottic and subglottic patients to be heavy drinkers of alcohol).[102, 103]

OTHER FACTORS

Laryngeal cancer is associated with nickel and mustard gas exposure.[104] There may also be association with asbestos exposure.[105, 106] Machinists and car mechanics are at increased risk.[107, 108] Long-term exposure to sulphuric and hydrochloric acid in battery plant workers is associated with an increased risk.[109] Postcricoid carcinoma is associated with previous radiation[93, 110] and sideropenic dysphagia.[93–95] Between 4% and 6% of patients have a history of Patterson-Brown-Kelly or Plummer—Vinson syndrome. Radiation is also implicated in posterior pharyngeal wall carcinomas.[111] Several studies associate high fruit and vegetable intake with a decreased risk of head and neck cancer. This may reflect increased intake of the antioxidants or free radical scavenging vitamins A, C and E.[112, 113] As in oral cavity and oropharyngeal cancer, HPVs may also be a factor in some cases of laryngeal and hypopharyngeal cancers. However, a causative role has been described in only small proportion of patients (5–30%).[114, 115] Laryngeal and hypopharyngeal cancers are also more common in people who are immunosuppressed due to HIV or organ transplantation.[116]

Cancer of the nasopharynx

Nasopharyngeal cancer (NPC) is rare with an incidence in the UK of 0.5/100 000[9], approximately 400 new cases every year.[117] It accounts for 1–2% of all head and neck cancers. In the United States there are approximately 2000 cases per year.[2] However, in southern China and Hong Kong the disease is endemic with an incidence rate of 50 per 100 000.[118] It is also common among Inuits of Alaska and in immigrant groups in the United States, such as recent Chinese immigrants and those from Southeast Asia such as the Hmong. In the last few years the rate at which Americans, including Chinese immigrants, have been developing this cancer has been slowly dropping.

According to the World Health Organization, there are three subtypes:[119] WHO type 1-keratinizing squamous cell carcinoma; WHO type 2-non-keratinizing (differentiated) carcinoma; and WHO type 3-undifferentiated carcinoma. In North America, type 1 accounts for 68% of cases.[120] In the Far East, types 2 and 3 account for 95% of cases.[121]

NPC is the result of interaction of genetic and environmental factors. The association is strongest for WHO types 2 and 3.[122] The genetic association is with different types of HLA types; in ethnic Chinese, NPC is associated

with HLA types A2, B17 and Bw46.[123, 124] HLA B17 carries the same risk as Bw46 and is associated with younger onset disease and poorer prognosis.[124, 125] In addition, family members of people with NPC are more likely to get this cancer. The most important environmental factor is infection by Epstein—Barr virus (EBV). Almost all NPC cells contain EBV.[126] There is a strong association between undifferentiated nasopharynx cancer and positive serology for EBV antigens. Antibody titres to EBV antigens correlate with stage of disease and a fall reflects tumour response to treatment whereas a rise in antibody levels means progression of disease.[126–128]

Dietary factors are also important. People who live in areas of Asia, northern Africa and the Arctic region, where NPC is common, typically eat diets very high in salt-cured fish and meat.[129] Studies indicate that foods preserved in this way that are cooked at high temperatures may produce chemicals that can damage DNA. Ho has reported accumulation of carcinogenic nitrosamines in salted fish.[130] In southeast China, the rate of this cancer is dropping as people begin eating a more 'Western' diet.

Cancer of the nasal cavity and paranasal sinuses

Cancers of the nasal cavity and paranasal sinuses are rare.[131] About 1200 people in the United States develop cancer of the nasal cavity and paranasal sinus each year, representing 3% of head and neck cancers.[132] Men are about 50% more likely than women to get this cancer. Nearly 80% of the people who get this cancer are between the ages of 45 and 85. About 60% to 70% of cancers of the nasal cavity and paranasal sinuses occur in the maxillary sinus, 20% to 30% in the nasal cavity, 10% to 15% in the ethmoid sinuses, and less than 5% in the frontal and sphenoid sinuses.[133]

As in all head and neck cancer, smoking tobacco is a risk factor for nasal cavity cancer. Occupational factors are also important. These include occupational exposure to dust from wood, textiles and leather and even perhaps flour.[134, 135] Other substances linked to this type of cancer are glues, formaldehyde, solvents used in furniture and shoe production, nickel and chromium dust, mustard gas, isopropyl ('rubbing') alcohol, and radium.[136] HPV infection has been reported in patients with benign and malignant tumour of the sinus.[137, 138] HPV DNA type 16 has been detected in over 50% of non-keratinizing carcinomas;[139] it likely represents a distinct histopathologic entity related to HPV infection. However, the clinical significance of these findings is not completely determined.

NON-SQUAMOUS MALIGNANT TUMOURS

Carcinoma of the thyroid

This is more common in women with a ratio of 3:1 and affects mainly young people with nearly two-thirds of cases in the age group 20–55 years. The commonest type is differentiated (80%) which includes papillary (85%) and follicular (15%) cancer. The poorly differentiated cancer accounts for 10% of cases, anaplastic 5% and medullary thyroid cancer 5%.[140] The incidence of thyroid cancer is increasing and this increase is mostly related to papillary carcinoma diagnosis, without any significant difference in the less frequent histologies. The increase is the result of the incidental detection of early thyroid cancer because of increasing use of imaging such as computerized tomography (CT), magnetic resonance imaging (MRI), ultrasound (US) and positron emission tomography (PET).[141] Between 1983 and 2006, the number of subcentimetre well-differentiated thyroid cancers (WDTC) increased five-fold. The incidence of WDTC > 2 cm and also larger WDTCs (> 4 cm and > 6 cm) at least doubled.[142] Therefore, the increase is due to subclinical diagnosis but also due to a true increase in disease incidence. The mortality rates for well differentiated thyroid cancer have remained relatively static and the prognosis is excellent with a 5-year survival of 97% of cases.[143] Thyroid cancer is more common in areas of the world where people's diets are low in iodine, and the opposite in areas with high iodine intake.[144, 145] However, there is not a strong epidemiological relationship between iodine intake and cancer and further studies are warranted.[146] A history of radiation treatment in childhood is a known risk factor. In the past, radiation was used to treat children with acne, fungal infections of the scalp, an enlarged thymus and tonsillar and adenoidal hypertrophy. Subsequent studies showed that there was an increased incidence of thyroid cancer in these children.[147] In contrast, exposure to radiation in adults carries little risk of thyroid cancer. Children exposed to radioactive fallout from nuclear power plant accidents or nuclear weapons also have an increased incidence of thyroid cancer. For example, children exposed to nuclear fallout from Chernobyl have an eight times incidence of thyroid cancer.[148–150]

Inherited medical conditions such as Gardner syndrome, familial polyposis and Cowden disease have an increased incidence of thyroid cancer. Certain families also have an increased incidence of papillary thyroid cancer. Medullary thyroid cancer (MTC), which constitutes approximately 5% of all thyroid malignancies, originates from the parafollicular C-cells, secretes calcitonin and occurs in both sporadic and hereditary forms.[151] Seventy-five per cent of MTC occurs as a sporadic form and 25% as a hereditary form. The hereditary forms can occur in three different settings: as a single component in a hereditary disease (FMTC); in the hereditary syndrome multiple endocrine neoplasia syndrome type A (MEN-2A) associated with parathyroid disease and phaeochromocytoma; and lastly in the hereditary syndrome MEN-2B associated with pheochromocytoma and a specific phenotype characterized by mucosal ganglioneuromas, intestinal ganglioneuromatosis and a marfanoid habitus. Both MEN-2 syndromes are autosomal dominant genetic disorders characterized by mutations in the *RET* proto-oncogene.[152, 153] Patients can now be stratified into high-, intermediate- and low-risk groups according to the type of *RET* mutation.[154]

Salivary gland carcinomas

There are two main types of salivary glands, the major salivary glands (parotid, submandibular and sublingual glands) and the minor salivary glands. About 80% of all salivary gland tumours are in the parotid gland, 10–15% in the submandibular gland and the rest in the sublingual and minor salivary glands.[140] Most tumours of the parotid gland are benign whereas 40% of submandibular gland tumours and 80% of minor salivary gland tumours are malignant. There are several different types of malignant tumours of the salivary glands due to the different types of cells that make up normal salivary glands. These include mucoepidermoid carcinoma, adenoid cystic carcinoma, acinic cell carcinoma, polymorphous low-grade adenocarcinoma and rare adenocarcinomas such as basal cell, clear cell, salivary duct and mucinous adenocarcinoma. Salivary gland carcinomas are not common and occur with an annual rate of 1.2 per 100 000 in the United States.[1] About one-third-of patients are under the age of 55 years. The incidence of these cancers is increasing but the cause for this is unknown.[155]

Exposure to radiation to the head and neck area for other medical reasons (e.g. radiotherapy for squamous cell cancer) increases the risk of salivary gland cancer.[156] Industrial exposure to radioactive substances and also accidental exposure from atomic bomb blasts also increase the risk of salivary gland cancer.[156] Some studies have also suggested that working with certain metals (nickel alloy dust) and minerals (silica dust) may increase the risk for salivary gland cancer. In men, smoking and heavy alcohol consumption was also associated with higher risk, but these factors were not strongly related to salivary gland cancer in women.[157] Hormonal dependence may also be important; early menarche and nulliparity are associated with increased risk, whereas older age at full-term pregnancy and long duration of oral contraceptive use are associated with reduced risk.[158] Female patients with salivary gland tumours are also 2.5 times more likely to develop breast cancer.[159] Diets low in vegetables and high in animal fat may also be important.[160]

Sarcomas of the head and neck

Sarcomas of the head and neck constitute less than 1% of head and neck malignancies.[161] They are divided into those arising from soft tissue (STS)[161] and those arising from bone (osteosarcoma).[162] STS comprise a heterogeneous group with varied histology and behaviour and include chondrosarcoma, dermatofibrosarcoma protuberans, Ewings sarcoma, leiomyosarcoma, liposarcoma, malignant fibrous histiocytoma, malignant peripheral nerve sheath tumour (MPNT), rhabdomyosarcoma and synovial sarcoma.[162] Rhabdomyosarcoma is rare in adults but is the most common STS in children with over 30% occurring in the head and neck. Dermatofibrosarcoma protuberans is a rare tumour of the dermis that has a high recurrence rate. Malignant fibrous histiocytoma is the most common STS in middle and late adulthood. Only 4% of liposarcomas occur in the head and neck with the neck being the most common site. Synovial sarcomas occur between the ages of 20 and 50 years with the majority arising in the parapharyngeal space. The most common site of chondrosarcoma in the head and neck is the larynx, followed by the maxilla and skull base. Most occur between the ages of 30 and 60 years. The most common site in the larynx is the posterior lamina of the cricoid cartilage (75%). MPNTs are extremely rare but more common in patients with neurofibromatosis type I (NF1).

Osteogenic sarcoma is a rare highly malignant tumour with an incidence of 1 in 100 000 with only 7% occurring in the head and neck region. The majority of these arise in the mandible followed by the maxilla. Head and neck osteosarcoma is most common between ages of 30 and 40 in comparison to long bone osteosarcoma, which is most common in teenage years.

GENETIC PREDISPOSITION

Studies have shown that some groups of individuals are at an increased risk of developing STS.[161, 163] Among them are genetically predisposed individuals, such as those suffering from neurofibromatosis who are at risk of MPNT, individuals with Li-Fraumeni syndrome, and children with retinoblastoma who are predisposed to osteosarcoma, rhabdomyosarcoma, and fibrosarcoma. Other heritable syndromes associated with an increased risk of STS include Gardner syndrome and nevoid basal cell carcinoma syndrome.

RADIATION, VIRUSES AND OTHER FACTORS

Previous exposure to irradiation is another well-documented risk factor[164] for both STS and osteogenic sarcoma. Although radiation-induced sarcoma (RIS) is a well-recognized long-term complication of radiation therapy for other sites, the head and neck is less commonly affected.[165] It is difficult to implicate therapeutic irradiation in the causation of head and neck tumours because of the inherent risk of multiple primary tumours in these patients. In addition, patients with certain types of primary tumours such as retinoblastomas have an increased sensitivity to radiation therapy, but are at increased risk for the development of sarcoma irrespective of the type of treatment.

Environmental carcinogens and chemicals like urethane, ethylene derivatives and polycyclic hydrocarbons have also been reported to increase the risk of STS at sites other than the head and neck.[166]

The role of viruses in the pathogenesis of STS has been investigated, but apart from the association of HIV with Kaposi's sarcoma and the observation that viral oncogenes such as the 'src' in the Rous sarcoma virus can transform cells in culture, no conclusive proof is available for a viral aetiology.[167] Immunosuppression attributable to either HIV infection or antirejection medication in organ transplant recipients may predispose children with latent EBV infection to leiomyosarcoma of the liver.

Patients with chronic lymphedema have an increased incidence of STS formation.[168] Patients with Paget's disease of bone, particularly the skull, are predisposed to osteogenic sarcoma.[169, 170]

KEY POINTS

- Squamous cell cancer is the most common head and neck malignancy, and it is related mainly to alcohol and tobacco use.
- Human Papilloma Virus (HPV) is now the leading cause of cancer of the oropharynx.
- Other malignancies of the head and neck such as thyroid cancer, salivary gland cancer and sarcomas are not related to alcohol or tobacco usage. The main causes of these cancers are less clear. Prior exposure to radiation in the head and neck area is one of the few identified risk factors.
- Genetic predisposition to head and neck cancer is rare and is present in a few inherited conditions such as Fanconi Anaemia and Li-Fraumeni Syndrome. Medullary thyroid cancer is a well-known example of a hereditary thyroid cancer secondary to a specific mutation in RET oncogene.
- There is an important role of head and neck cancer prevention through alcohol and tobacco cessation, HPV vaccination and close follow-up of risk groups such as genetic conditions carriers.

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CHAPTER 3

EPIDEMIOLOGY OF HEAD AND NECK CARCINOMA

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SEARCH STRATEGY

Data in this chapter may be updated by a PubMed search using the keywords: oral cavity, oropharyngeal cancer, laryngeal cancer, hypopharyngeal cancer, nasopharyngeal cancer, squamous cell carcinoma, HPV, EBV, smoking, alcohol, and/or epidemiology.

INTRODUCTION

Head and neck cancer comprises a diverse array of diseases with distinct anatomical subsites, histopathologic features and risk factors. The most common type of head and neck cancer is squamous cell carcinoma (SCC) of the mucosa of the upper aerodigestive tract (UADT). In 2008, more than 600 000 people worldwide were diagnosed with UADT SCC.[1] The incidence of and risk factors for UADT SCC differ by tumour subsite. The five major subsites are nasopharynx, oral cavity, oropharynx, larynx, and hypopharynx.

Nasopharyngeal cancers are typically related to Epstein–Barr virus, and are a major contributor to the UADT burden in Southern China and Southeast Asia. However, SCCs at this site are relatively rare in other populations. The majority of UADT SCCs worldwide were caused by tobacco and alcohol, and in many countries, public health efforts aimed at reducing tobacco exposure have helped decrease the incidence of UADT SCC. However, in North America, Europe and Australia, there is an epidemic of oropharyngeal SCC (OPSCC) caused by infection with human papillomavirus (HPV), and HPV-positive OPSCC is now more common than tobacco-and-alcohol-associated OPSCC in many of these countries.[2] In contrast, in developing countries where the prevalence of smoking is increasing, the incidence of UADT SCC is also increasing. The rate of oral cavity SCC is higher in South Asian countries than other countries, most likely because of use of oral tobacco and related products, resulting in a global health disparity.

This chapter discusses the incidence of and risk factors for SCC of the oral cavity, oropharynx, larynx and hypopharynx. The shift from tobacco-and-alcohol-related to HPV-related OPSCC is also examined, along with the associated health implications and global variations. A more comprehensive treatment of aetiology is discussed in Chapter 2, Aetiology of head and neck cancer.

SCC OF THE ORAL CAVITY

Worldwide, SCC of the oral cavity is the tenth most common cancer among men, and in 2008, 263 000 people were diagnosed with this disease (171 000 men and 92 000 women).[1] The majority of oral cavity SCCs are related to tobacco and alcohol exposure (61% of oral cavity SCCs in Europe, a higher proportion in India).[3] There is a dose-effect relationship between tobacco and alcohol exposure and risk of oral cavity SCC, and individuals exposed to high levels of tobacco and alcohol have an odds ratio of 7.1 (95% confidence interval [CI], 5.0–10.0) compared to those without tobacco or alcohol exposure.[4] In the United States, because of public health initiatives, the rate of current cigarette smoking declined from 43% in 1965 to 21% in 2004, and in the past three decades there has been a concomitant decrease in the overall rate of oral cavity SCC.[5,6] Globally, as the use of tobacco in developing countries has increased, there has been a subsequent increase in the incidence of oral cavity SCC.[7] Hence, while oral cavity cancer is the tenth most common cancer among men worldwide,

its incidence varies with the prevalence of tobacco use and is higher in many developing countries and lower in many developed countries.

The oral cavity is anatomically subdivided into the oral tongue, floor of mouth and gingivobuccal subsites. In developed countries, the typical patient with oral cavity SCC is a man in the sixth-to-seventh decade of life with a history of smoking and alcohol exposure and a tumour located on the lateral tongue or floor of mouth. These two subsites are the most common subsites of oral cavity SCC; in a National Cancer Database review by Funk et al, 32% of oral cavity SCCs occurred in the lateral tongue and 28% occurred in the floor of the mouth.[8] Oral cavity SCCs are likely to be associated with occult nodal metastasis at presentation, and therefore many patients present with advanced disease.

There is one notable exception to the pattern of decreasing incidence of oral cavity SCC in developed countries: among white patients younger than 40 years in the United States, there has been a 2% annual increase in the incidence of SCC of the oral tongue, though such tumours in young patients are exceptionally rare.[9, 10] Some Scandinavian countries have shown similar increase in incidence of young patients with oral tongue cancer.[11] The explanation for this phenomenon is unclear: not all affected patients have a history of prolonged tobacco exposure, and there is no known viral or other cause for the increase in incidence. Clinical tumour behaviour and survival rates in these young patients with oral cavity SCC mimic clinical tumour behaviour and survival rates in their older counterparts.[12, 13]

Use of smokeless tobacco, tobacco with or without additives that is dipped or chewed, is also a risk factor for oral cavity SCC. Because of global variation in the prevalence of smokeless tobacco use (ranging from less than 5% in the United States to more than 1 in 3 males in India), concurrent smokeless tobacco use and cigarette use, and regional variation in potentially carcinogenic additives, determination of the exact contribution of smokeless tobacco to the risk of oral cavity SCC is difficult.[14, 15] Boffetta et al pooled data from multiple studies and estimated a summary relative risk of 1.8 (95% CI, 1.1–2.9) for users of smokeless tobacco compared to non-users.[15]

Betel nut is an additional risk factor for oral cavity SCC, particularly in developing countries. Betel nut, from the betel or areca palm tree, can be chewed alone or mixed with tobacco and lime and placed in a betel-leaf pouch (in India this is called paan, and there are many variations). Absorption of the red juice produced by the betel mixture results in cholinergic stimulation in the short term but carcinogenesis over the long term. Betel nut use is common throughout South Asia, though exact usage rates are difficult to determine. In India, in 2010, oral cavity SCC was the number one cause of death for men over the age of 30 years, and in 2008, oral cavity SCC was the most common cancer diagnosed in men, in part due to use of betel nut and smokeless tobacco.[16–18]

Oral cavity SCC related to betel nut use most commonly occurs in the buccal mucosa, whereas oral cavity SCC related to tobacco and alcohol use most commonly occurs in the oral tongue or floor of mouth.[19, 20] Betel nut may also cause a benign but devastating submucosal fibrosis of the buccal mucosa, which in severe cases can cause trismus and hinder eating; in some cases, this submucosal fibrosis may be premalignant.[21]

Other risk factors may play a role in oral cavity SCC: multiple studies have examined the role of marijuana as a risk factor; however, no conclusive evidence has been found implicating marijuana use as a cause of UADT SCC at any subsite.[22] These studies may suffer from recall bias, subsite misclassification, confounding due to concurrent tobacco use, and low incidence of heavy marijuana use, and further investigation is needed.[23] Poor oral hygiene has also been identified as a potential risk factor but may be a sign of disease rather than a cause. Defective DNA repair pathways may also play a role in the development of SCC.[24] While HPV plays a strong role in the etiology of OPSCC, there is no evidence that HPV contributes to any great degree to oral cavity SCC.

Patients with Fanconi anaemia are at higher risk than the general population for developing oral cavity SCC.[25] Fanconi anaemia is caused by an autosomal recessive genetic mutation. The disease manifests as congenital anomalies (most commonly skeletal, renal and developmental) and progressive pancytopenia and results in a shortened life expectancy. Leukemia is the most common associated cancer, and there is also an increased risk of head and neck cancers. These occur at a younger age than typical tobacco-related head and neck cancers, most often occur in the oral cavity, and may be aggressive.[25]

SCC OF THE OROPHARYNX

UADT SCC has traditionally been strongly associated with tobacco and alcohol exposure. In the United States, it was expected that the incidence of OPSCC would decrease in parallel with decreasing smoking rates, but in fact, there was only a plateau in OPSCC incidence followed more recently by a dramatic increase.[6, 26, 27] Closer examination revealed that the increase occurred in middle-aged white men, while the incidence of OPSCC in men older than 60 years of all races was decreasing. Furthermore, the middle-aged men who were developing OPSCC often had no history of smoking or were former or light smokers. Because of multiple lines of evidence, the increasing OPSCC incidence in this group is now attributed to HPV.

Two molecularly and epidemiologically distinct types of OPSCC are now recognized, classified according to HPV status. HPV-negative OPSCC is epidemiologically similar to the traditional type of UADT SCC, in which long-term exposure to tobacco and alcohol leads to development of malignancy. The typical patient with HPV-negative OPSCC is a man older than 55 years with a long history of smoking and drinking and a well or moderately differentiated SCC. HPV-negative OPSCC is declining in incidence in the United States, similar to what is occurring with respect to the incidence of other SCCs of the UADT that are caused by tobacco and alcohol but not HPV (SCCs of the oral cavity, larynx and hypopharynx).[2, 28]

In contrast, the typical patient with HPV-positive OPSCC is a middle-aged, non-smoking white man from a higher socioeconomic status and with a history of multiple sexual partners.[29]

HPV-positive OPSCC originates with exposure to high-risk HPV, a sexually transmitted virus, and can develop independently of tobacco or alcohol exposure.[28, 30] HPV is most strongly associated with OPSCC found at the tonsil and base of tongue, and cancers at these subsites account for an increasing proportion of all OPSCCs.[31] Oropharyngeal HPV infection is a necessary event in the development of HPV-positive OPSCC.[30] Although HPV can also be transmitted by less intimate skin-to-skin contact, HPV is transmitted primarily via sexual contact, and the risk of oral cavity/oropharyngeal HPV infection increases with the number of oral sexual partners.[32] The current literature shows that at any given time, approximately 7% of the population has a prevalent oral cavity/oropharyngeal HPV infection.[33, 34] The lifetime oral exposure rate is unknown, but an estimated 65% to 100% of sexually active adults have been exposed to HPV at either anogenital or oropharyngeal sites.[35, 36] Given the high point prevalence of oral/oropharyngeal HPV infection, most such HPV infections are cleared by the immune system and do not progress to cancer. Delayed clearance of oral/oropharyngeal HPV infection may be a risk factor for development of OPSCC, just as prolonged/chronic cervical HPV infections are associated with subsequent cervical cancers.

HPV exposure is so common that the presence of HPV DNA in malignant tissues does not establish causality; for example, a patient with a heavy smoking and drinking history may have a tobacco-induced cancer but also have HPV DNA found in the tumour. However, a cell that has become malignant due to HPV oncogenesis will typically overexpress *p16*. *TP53* is commonly mutated in tobacco-related cancers of the UADT, but *TP53* mutations are not common in HPV-related OPSCC. Therefore, p16 staining and determination of *TP53* mutation status can help distinguish truly HPV-related cancers from cases in which HPV DNA is detectable but the cancer is not HPV-related and cases in which detection of HPV DNA represents a false positive result.

There has been some confusion regarding the role of HPV in UADT SCC at sites other than the tonsil and base of tongue. While HPV DNA has been identified in SCC at other UADT subsites, the causal role of HPV in carcinogenesis at these subsites has not been established, and the proportion of cancers at these other subsites attributable to HPV is likely small. Given the high rates of exposure to HPV, the mere presence of HPV DNA alone cannot support causality. HPV-related oncogenic proteins and downstream events such as *p16* overexpression must be detected as part of proving causality. Additionally, poor classification of the tumour subsite, as well as overlap of some subsites, may also have led to misclassification, particularly in older published studies. For instance, whereas previously some OPSCCs (particularly those of the base of tongue, which are often coded as a generic site 'tongue') were misclassified as oral cavity SCCs, classification of tumour sites has been improving and, in parallel, HPV positivity rates for non-oropharyngeal cancers of the UADT have dropped over time, while HPV positivity rates for OPSCC have risen.[37] Differences in testing methods for HPV may also have contributed to high rates of false-positive findings. Regardless, the rate of HPV-positive SCC has consistently been higher in the oropharynx than in the oral cavity, larynx or hypopharynx.[27]

The incidence of HPV-positive OPSCC is increasing markedly, and it is not hyperbole to call this an epidemic. An estimated 85 000 cases of oropharyngeal cancer occurred worldwide in 2008, and at least 22 000 of these were HPV positive.[38] From 1988 to 2004, there was a 225% population-level increase in HPV-positive OPSCC in the United States (from 0.8 cases per 100 000 individuals in 1988 to 2.6 per 100 000 in 2004) and a concomitant 50% decrease in HPV-negative OPSCC (from 2.0 cases per 100 000 individuals in 1988 to 1.0 per 100 000 in 2004[2, 39] (**Figure 3.1**). In the United States, the percentage of OPSCC cases that were HPV-positive increased from 16% in 1984–89 to over 70% in 2000–04. There has been a 5% annual percentage rate increase in the incidence of OPSCC in the United States and a 6% increase in Finland.[2, 39] Chaturvedi et al estimated that by 2020 the incidence of HPV-positive OPSCC will be greater than

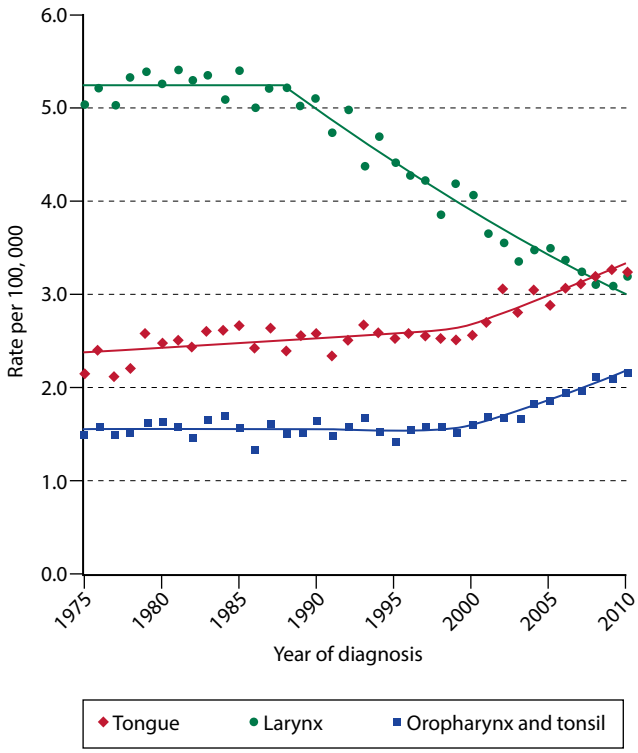

Figure 3.1 Age-adjusted SEER incidence rates by cancer site 1975–2010 (all ages, all races and both sexes). Cancer sites include invasive cases only, unless otherwise noted. Rates are per 100 000 and are age-adjusted to the 2000 US Std Population (19 age groups – Census P25-1130). Regression lines are calculated using the Joinpoint Regression Program Version 4.0.3, April 2013, National Cancer Institute. Incidence source: SEER 9 areas (San Francisco, Connecticut, Detroit, Hawaii, Iowa, New Mexico, Seattle, Utah and Atlanta).

the incidence of cervical cancer, and by 2030, more than half of all head and neck cancers will be related to HPV.[2] The increase in HPV-related OPSCC is well documented in North America, Europe and Australia although marked geographical variation is evident.[2, 40–42] For example, recent data from the UK[43] in a multicentre study involving the HPV typing of tumour samples from ~1400 patients treated between 2002 and 2011, confirmed that whilst the incidence of oropharynx cancer doubled, the prevalence of cases attributable to HPV infection remained stable at ~55% during this decade. Consideration of these, somewhat surprising, data leads to a conclusion that HPV-negative oropharynx cancer has also been increasing in the UK throughout this time period, despite the overall population reduction in tobacco smoking. Why this is, is a matter of conjecture but the authors, citing the parallel increase in oral cavity tumours, suggest a potential role for increased alcohol consumption. Moreover, a similar increase in HPV-positive OPSCC has not been well documented in South America, Africa and Asia, but population-based studies from these regions with careful site classifications and exposure data are limited or non-existent, and different sexual practices and continued high smoking rates may also obscure these trends.

In 2008, using the Surveillance, Epidemiology and End Results (SEER) database (1973–2004), which contains information on a sample of patients in the United States, Chaturvedi et al demonstrated in a landmark study that the rise of OPSCC incidence was occurring specifically among middle-aged white men.[6] There were no significant changes in OPSCC incidence among individuals under 40 years or over 59 years of age, but among middle-aged white men, a 10% annual increase in incidence was seen since 2000.[6] Mehta et al utilized the SEER database to compare the incidence of OPSCC in different age groups during the period from 1973 through 2006.[26] They found that the proportion of patients aged 40–59 years increased from 35% to 45%, while the proportion of oropharyngeal cancer patients aged 60–79 years decreased from 52% to 40%.[26] The increase in OPSCC incidence among Caucasian males is so dramatic as to nearly obliterate a previous racial disparity in the incidence of UADT SCC.[44] In the late 1980s, African American males had more than twice the incidence of OPSCC of white American males; this disparity has been completely eliminated by the increase in OPSCC among white men and continued decrease in OPSCC incidence among African American men.[6]

Patients with HPV-positive OPSCC are less likely to have a history of tobacco exposure; in most series of patients with OPSCC, about 30% of patients in the HPV-positive group are non-smokers, compared with fewer than 5% of patients in the HPV-negative group.[45] Patients with HPV-positive OPSCC are also less likely to use alcohol than are patients with HPV-negative OPSCC patients or those with SCC at other subsites of the head and neck.[46] The past few decades have seen a decrease in the age of sexual debut and an increase in the number of sexual partners, contributing to HPV exposure.[47] However, demographic, exposure and behavioural factors are only somewhat predictive of HPV status in patients with OPSCC and should not replace HPV testing.[48]

Patients with HPV-positive OPSCC are more likely to present with small primary tumours and more extensive and possibly cystic nodal disease.[49] Patients with HPV-positive OPSCC may also present at a younger age than the typical head and neck cancer patient, and thus complaints of neck mass or other symptoms related to the UADT should be carefully evaluated. Finally, HPV-related OPSCC tumour histology is more likely to be basaloid, lymphoepithelial or poorly differentiated.[50] Even though patients with HPV-positive OPSCC are more likely to present with advanced nodal disease, survival is better in patients with HPV-positive OPSCC than in those with HPV-negative OPSCC, which is further discussed in Chapter 13, Oropharyngeal tumours.[49, 51–53]

Over 90% of HPV-positive OPSCC cases are caused by a single HPV type, HPV 16, and few OPSCC cases can be attributed to the other HPV types.[54] This has implications for future public health efforts to decrease HPV-positive OPSCC via vaccination. In the United States, two current Food and Drug Administration-approved HPV vaccines provide strong protection against infection with HPV 16. These vaccines are directed towards the viral capsid L1 or L2, a late protein that is expressed during infection and prior to carcinogenesis. Currently these HPV vaccines are approved in the United States for prevention of cervical cancer and prevention of genital warts and anal cancer in both men and women.[55] There is not currently an indication for prevention of HPV-positive OPSCC, as no studies have been conducted to evaluate the effect of the vaccine on oral/oropharyngeal HPV infection and OPSCC development. Given the decades-long delay between HPV exposure and carcinoma detection, such a study will be difficult and costly. However, because HPV 16 is the cause of the overwhelming majority of HPV-positive OPSCC, it is likely that the vaccine will prevent HPV 16 oropharyngeal infection and subsequent OPSCC development when given to individuals prior to HPV 16 exposure.

SCC OF THE LARYNX

In 2008, 150 000 people worldwide were diagnosed with laryngeal SCC.[1] The majority of patients with laryngeal SCC are men. Laryngeal SCC is strongly related to smoking and alcohol use; multiple studies confirm that the risk in smokers and drinkers is 4–177 times the risk in non-smokers/non-drinkers and that risk increases with duration and frequency of exposure.[3, 56–58] Alcohol or tobacco exposure alone are also significant risk factors for the development of laryngeal SCC.[57] In the United States, the incidence of laryngeal SCC plateaued in 1992 and then decreased 2.8% per year from 1992 through 2009 (to an age-adjusted incidence rate of 3.4/100 000 in 2006–10) as tobacco control efforts began to show an effect, and similar changes were seen across Europe.[27, 59–62] In developing countries, as smoking rates

have increased there has been a concomitant increase in the incidence of laryngeal SCC.[7]

The larynx is divided into supraglottic, glottic and subglottic sites, and the presentation of laryngeal SCC differs by subsite. Supraglottic and glottic carcinoma are the most common and make up over 90% of all laryngeal SCC.[63] Because of their rarity, subglottic cancers are often excluded from analysis. More than 50% of laryngeal SCC arise in the glottis, and such cancers tend to occur in heavy smokers who present early in the course of disease with hoarseness.[56, 58, 64] Because of the paucity of lymphatics in the glottic region, many glottic cancers do not have regional metastasis. Supraglottic lesions make up about 32–35% of laryngeal SCC, tend to occur in people who use alcohol and tobacco and, in contrast to glottic lesions, are more likely to present late with extensive nodal disease due to the rich bilateral lymphatic supply of the supraglottic area and the lack of identifying symptoms associated with small supraglottic lesions.[63–65] Perhaps because of the early presentation of glottic lesions, the survival rate is better among patients with glottic SCC than among those with supraglottic SCC.

Other factors have been implicated in the aetiology of laryngeal SCC, particularly among individuals who do not smoke or use alcohol. Laryngeal SCC may be related to laryngopharyngeal reflux disease or gastro-oesophageal reflux disease, although studies conflict and most are retrospective and may suffer from recall bias and misclassification of reflux disease status.[66–69] Occupational and environmental exposures in the form of inhalation of potentially toxic fumes have also been implicated. These include exposure to diesel exhaust, wood oven smoke, second-hand smoke and asbestos, but the extent of risk is unclear.[70]

SCC OF THE HYPOPHARYNX

The hypopharynx is the least commonly affected of the five major UADT anatomical subsites.[71] Exact numbers of SCCs of the hypopharynx are difficult to determine because in many cancer registries, hypopharyngeal sites are combined with oropharyngeal sites. The hypopharynx is made up of the piriform sinuses bilaterally, the posterior pharyngeal wall and the postcricoid area; the piriform sinus is the subsite most commonly affected. The majority of patients with hypopharyngeal SCC are male (76–80%) and older than 50 years (93–95%) (mean age at diagnosis, 65 years) with a history of smoking and drinking; patients with hypopharyngeal SCC report more excessive use of alcohol than patients with laryngeal SCC.[72, 73] Patients with hypopharyngeal SCC also tend to present late when there is already nodal metastasis, and a Canadian study showed that 80% of patients presented with nodal metastasis and 19% of patients presented with unresectable disease.[73] The distant metastasis rate is higher for hypopharyngeal SCC than for laryngeal or oral cavity SCC: the rate of distant metastasis is 25% at 1 year after completion of initial treatment.[73]

Given the relatively small numbers of patients with hypopharyngeal SCC, as well as the grouping together of multiple pharyngeal sites in reports using data from large cancer databases, there is little published information on hypopharyngeal SCC incidence rates and changes in such incidence attributable to tobacco control efforts. The SEER database shows a slight decrease in the incidence of hypopharyngeal SCC between 1974 and 1999, from 1.0/100 000 to 0.8/100 000.[74]

SUMMARY

The majority of UADT SCCs are related to smoking and drinking, the major exception being HPV-related OPSCCs. In countries where the smoking rate is decreasing, the incidence of UADT SCC is also decreasing. In developing countries, increasing rates of tobacco use are causing a rise in the incidence of UADT SCCs. Tobacco and related products are responsible for oral cavity cancers being the most common cancer in India. Efforts to curb tobacco use should be aimed at high-risk populations. The epidemic of HPV-positive OPSCC necessitates that practitioners be aware of the changing demographics of OPSCC. Future health efforts to increase vaccination against HPV are critical for stemming the increase in OPSCC incidence.

KEY POINTS

- The incidence of laryngeal and hypopharyngeal SCC has decreased after successful implementation of public health efforts aimed at tobacco control.
- In North America, Europe and Australia, there is an epidemic of HPV-positive OPSCC, particularly among middle-aged men, and this epidemic is likely related to sexual behaviours.
- Oral cavity cancer is the most common cancer in India, where the common use of oral tobacco and betel nut is the principal cause.
- The epidemiology of SCC of the UADT differs radically by anatomical subsite.
- HPV is a causative factor for OPSCCs, and these cancers often occur among middle-aged men who do not smoke or drink. There is an epidemic of HPV-related OPSCC in North America, Europe and Australia, and it is most often attributed to prior HPV 16 infection; vaccination against HPV 16 may decrease the incidence of OPSCC in those vaccinated prior to exposure to HPV 16.
- Oral cavity SCC, laryngeal SCC, and hypopharyngeal SCC are most often related to smoking and drinking. Tobacco control efforts are decreasing the incidence of these three cancer types.
- Other risk factors may also play a role in SCC of the UADT, such as environmental exposures, concurrent diseases, and defects in DNA repair mechanisms.

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CHAPTER 4

STAGING OF HEAD AND NECK CANCER

Nicholas J. Roland

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SEARCH STRATEGY

The data in this chapter are supported by a Medline search using the key words staging of head and neck cancer. The author also consulted the International Union Against Cancer booklet TNM classification of malignant tumours, eighth edition[1] and AJCC cancer staging manual, eighth edition.[2] The nature of staging has meant that the data to support the concept have been largely drawn from retrospective and observational studies (level 3). Much of the systems development has been through the opinion of expert panels using these data (level 4).

INTRODUCTION

There are many aspects that affect the outcome of patients with a malignant head and neck tumour. These relate to the tumour (the anatomical site and the clinical and pathological extent of the disease), the host (age, general condition and any intercurrent disease of the patient) and management (treatment options, expertise available, patient preference). Concurrently, there are also many proposed systems that try to evaluate these factors and predict outcomes for an individual patient.

Staging of head and neck cancer is a system designed to express the relative severity, or extent, of the disease. It is meant to facilitate an estimation of prognosis and provide useful information for treatment decisions. Classification by anatomical extent of the disease, as determined clinically and histopathologically (when possible), is that with which the tumour, nodes, metastases (TNM) system primarily deals. The concept is that an orderly progression of disease takes place with enlargement of and invasion by the primary tumour (T) followed by spread to the regional lymph nodes (N) and eventually spread beyond these nodes to distant meta- static sites (M). The stage at diagnosis in the life history of an individual cancer is numerically assigned a TNM classification. These individual TNM classifications are then assembled into four groups – stage groups (stages I–IV), each with similar survival outcomes based on the observation that better survival is anticipated for cancers with less extension.

AIMS OF THE TNM STAGING SYSTEM

There are many benefits to staging, but one of the principal purposes is to provide a method of conveying clinical experience to others without ambiguity (**Box 4.1**).

The strengths of the TNM staging system are its simplicity, low cost, relative accuracy, objectivity, universal acceptance and lack of need for special technology. But the system is not without limitations. Inconsistencies, observer variability and differences in stage method contribute to potential bias. Uniformity in the method of data collection, knowledge of the current TNM system and accurate application of the correct stage are therefore pivotal if meaningful information is to be derived.

BOX 4.1 Objectives of staging

1. To aid the clinician in the planning of treatment
2. To give some indication of prognosis
3. To assist in evaluation of the results of treatment
4. To facilitate the exchange of information between treatment centres
5. To contribute to the continuing investigation of human cancer

HISTORY AND DEVELOPMENT OF STAGING

The TNM staging system has developed with contributions from both sides of the Atlantic.

In Europe, Pierre Denoix developed the TNM system for the classification of malignant tumours between the years 1943 and 1952.[3] During the 1950s the International Union Against Cancer (UICC) appointed a Committee on Tumour Nomenclature and Statistics. Agreement was reached on a general technique for classification by anatomical extent of the disease, using the TNM system. In 1958, laryngeal and breast cancer were the first primary sites to be assigned recommendations on clinical stage and presentation of results.[4] A decade later, the first TNM booklet, the 'Livre de poche', was published.[5] Over the years, series of meetings have been held to update and unify existing classifications as well as to develop new ones.

In the United States, the initial staging system proposed by the American Joint Committee on Cancer (AJCC) in the late 1960s and implemented in the mid-1970s was simply based on a 'consensus' of leaders and experts in the specialty who were members of the working group of what was then called The American Joint Committee for Cancer Staging and End-Results Reporting. They reviewed the available literature of that time and added their own experiences to devise the initial staging system. Subsequent revisions were also implemented based on the observations of the committee members on information available in the literature and from institutional experiences.

In 1983, The American Joint Committee for Cancer Staging and End-Results Reporting became the now familiar AJCC. Since 1996, the current AJCC Head and Neck Task Force has utilized the data from the National Cancer Data Base (NCDB). This is maintained by the Commission on Cancer of the American College of Surgeons and supported by the American Cancer Society as well as data from Surveillance, Epidemiology and End Results Reporting (a database maintained by the National Cancer Institute, which represents 14 cancer registries). In addition to this, data from state cancer registries are also used on occasion. Review of the literature is performed by the task force, who are all selected for their breadth of expertise and depth of knowledge, to incorporate new information and/or new data, which may impact upon revisions on the staging process.

The eighth edition of the UICC and American Joint Committee on Cancer (AJCC) Staging Manual, Head and Neck Section introduces significant modifications from the prior seventh edition. The most significant update creates a separate staging algorithm for high-risk human papilloma virus associated cancer of the oropharynx, distinguishing it from oropharyngeal cancer from other causes. Other modifications include: the reorganization of skin cancer (other than melanoma and Merkel cell carcinoma) from a general chapter for the entire body to a head and neck-specific cutaneous malignancies chapter; changes to the tumour (T) categories for oral cavity, skin, and nasopharynx; and the addition of extranodal cancer extension to lymph node category (N) in all but the viral-related cancers and mucosal melanoma. One other key change from prior editions of the TNM system is the elimination of the T0 category in sites other than the nasopharynx, HPV-associated oropharyngeal cancer, and salivary gland cancers (which can be identified by their unique histology). If no primary lesion can be identified, then the lymph node may have emanated from any mucosal site, so it is considered that there is no rationale to support retaining the T0 designation outside of the virally associated cancers of the oropharynx and nasopharynx.[1, 2, 6, 7] Thyroid staging has been altered with a change in the increased risk age from 45 to 55 years.

The UICC contains rules of classification and staging that correspond exactly with those appearing in the AJCC cancer staging manual and has approval of all national TNM committees.[1, 2]

GENERAL RULES FOR STAGING

The TNM system for describing the anatomical extent of the disease (**Table 4.1**) is based on three components:

- T – extent of the primary tumour
- N – absence or presence and extent of regional lymph node metastases
- M – absence or presence of distant metastases.

All cases should be confirmed microscopically. Two classifications should be documented for each site, namely: clinical (pre-treatment) classification (cTNM), and pathological (post-surgical histopathological) classification (pTNM). The clinical stage is essential to select and evaluate therapy, while the pathological stage provides

TABLE 4.1 The TNM system for describing the anatomical extent of the disease

T – Primary tumour		N – Regional lymph nodes		M - Distant metastasis	
TX	Primary tumour cannot be assessed	NX	Regional lymph nodes cannot be assessed	MX	Distant metastasis cannot be assessed
T0	No evidence of primary tumour	N0	No evidence of regional lymph node metastases	M0	No distant metastasis
Tis	Carcinoma in situ	N1, N2, N3	Increasing involvement of regional lymph nodes	M1	Distant metastasis
T1, T2, T3, T4	Increasing size and/or local extent of the primary tumour				

the most precise data to estimate prognosis and calculate end results. It should be remembered that if there is doubt concerning the correct T, N or M category to which a particular case should be allocated, then the **lower** (i.e. **less advanced**) category should be chosen. Midline nodes are considered ipsilateral except in thyroid cancers. After assigning the cTNM and pTNM categories, the patient should then be classified into a stage group. Once established this must remain unchanged in the medical records. The eighth edition recommends a prognostic factors classification and uses a 'prognostic factors grid' for each subsite.[8] This relates three prognostic factors grouped to relate to the 'tumour' (e.g. T and N stage, level of nodes), the 'host' (e.g. performance status, comorbidity, age) and the 'environment' (e.g. expertise, quality of treatment) under the narrative of essential, additional and new and promising.[1, 2, 8]

The TNM classification applies only to carcinomas and the following sites are included:

- lip and oral cavity
- pharynx: oropharynx (p16-negative and p16-positive), nasopharynx, hypopharynx
- larynx: supraglottis, glottis, subglottis
- nasal cavity and paranasal sinuses (maxillary and ethmoid sinus)
- unknown primary carcinoma – cervical nodes
- malignant melanoma of upper aerodigestive tract
- major salivary glands
- thyroid gland.

Carcinomas arising in minor salivary glands of the upper aerodigestive tract are classified according to the rules for tumours of their anatomic site of origin (e.g. oral cavity). Each site is described, with rules for classification, anatomical sites and subsites where appropriate, the cTNM classification, the pTNM classification, G histopathological grading, stage grouping and a summary. The main aspects are described here, but specific details can be found in the most recent UICC/AJCC TNM booklets.[1, 2]

Histopathological grading

The histological grading of squamous cell carcinoma represents estimation by the pathologist of the expected biological behaviour of the neoplasm. It has been suggested that such information in conjunction with other characteristics of the primary tumour would be useful in the rational approach to therapy.[8] Others have reserved doubts as to the validity of the method because of its subjective nature.[9, 10] Although grading of squamous cell carcinoma of the upper aerodigestive tract mucosa is a common practice, it has not evolved as an important factor in planning therapeutic strategies.

In a systematic review of 3294 patients, it was found that 46% of patients with poorly differentiated tumours had a nodal metastasis at presentation compared with only 28% of differentiated tumours. Distant metastases at presentation were found in 3.4% of poorly differentiated tumours compared with 1.8% of well-differentiated tumours. Primary and nodal recurrence rate rose and survival fell significantly for poorly differentiated tumours.[11] In another retrospective review of more than 1000 patients, grade and distant metastases were considered. It was found that patients with well-differentiated tumours are at low risk of metastases and patients with poorly differentiated tumours are at high risk of distant metastases. It was suggested they should be considered for systemic chemotherapy.[12] Although histological differentiation is subject to inter- and intraobserver error, it is still worthwhile in clinical practice and, therefore, remains an adjunctive part of the TNM system.[1, 2]

The definitions of the G categories apply to all head and neck sites apart from thyroid. They are shown in **Box 4.2**.

BOX 4.2 G = Histopathological grading

GX: Grade of differentiation cannot be assessed
G1: Well differentiated
G2: Moderately differentiated
G3: Poorly differentiated
G4: Undifferentiated

Additional descriptors

When sentinel lymph node biopsy is attempted, designation is now applicable using the suffix 'sn' after N stage. The absence or presence of residual tumour after treatment may be described by the symbol 'R'. A recurrent tumour, when classified after a disease-free interval is identified by the prefix 'r'. The prefix 'a' indicates that classification is first determined at autopsy.

The certainty factor, or C factor, has now been dropped from the introduction rules on staging but is still worthwhile considering during the diagnostic workup. It reflects the validity of classification according to the diagnostic methods employed (C1–C5). C1 is evidence from standard diagnostic means whereas C5 is evidence from autopsy. Pretherapeutic clinical staging of head and neck cancers should be based on a C2 factor, evidence obtained by special diagnostic means such as radiographic imaging (e.g. computed tomography (CT), magnetic resonance imaging (MRI) or ultrasound scan), endoscopy, biopsy and cytology.[1, 2]

Stage grouping

A tumour with four degrees of T, three degrees of N and two degrees of M will have 24 potential TNM categories. It has, therefore, been felt necessary to condense these into a convenient number of TNM stage groups (**Table 4.2**). The grouping adopted is designed to ensure, as far as possible, that each group is more or less homogenous in respect of survival and in addition, that the survival rates of these groups for each cancer site are distinctive. Carcinoma *in situ* is categorized as stage 0, cases with distant metastases as stage IV. The exception to this grouping system are p16-positive oropharyngeal, nasopharyngeal and thyroid cancers (**Tables 4.3, 4.4, 4.5a, 4.5b** and **4.5c**).[1, 2]

TABLE 4.2 Stage grouping

Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T1, T2	N1	M0
	T3	N0, N1	M0
Stage IVA	T1, T2, T3	N2	M0
	T4a	N0, N1, N2	M0
Stage IVB	Any T	N3	M0
	T4b	Any N	M0
Stage IVC	Any T	Any N	M1

TABLE 4.3 Stage grouping HPV (p16-positive) related oropharyngeal cancer

Stage I	T1, T2	N0, N1	M0
Stage II	T1, T2	N2	M0
	T3	N0, N1, N2	M0
Stage III	T1-T3	N3	M0
	T4	Any N	M0
Stage IV	Any T	Any N	M1

TABLE 4.4 Stage grouping for nasopharynx

Stage I	T1	N0	M0
Stage II	T1	N1	M0
	T2	N0-1	M0
Stage III	T1-2	N2	M0
	T3	N0-2	M0
Stage IVA	T4	N0-2	M0
Stage IVB	Any T	N3	M0
Stage IVC	Any T	Any N	M1

TABLE 4.5a Stage grouping for medullary thyroid carcinoma

Stage I	T1a, T1b	N0	M0
Stage II	T2, T3	N0	M0
Stage III	T1, T2, T3	N1a	M0
Stage IVA	T1, T2, T3	N1b	M0
	T4a	Any N	M0
Stage IVB	T4b	Any N	M0
Stage IVC	Any T	Any N	M1

TABLE 4.5b Stage grouping for differentiated thyroid carcinoma

Papillary or follicular *Under 55 years*			
Stage I	Any T	Any N	M0
Stage II	Any T	Any N	M1
Papillary or follicular *55 years and older*			
Stage I	T1a, T1b, T2	N0	M0
Stage II	T3	N0	M0
	T1, T2, T3	N1	M0
Stage III	T4a	Any N	M0
Stage IVA	T4b	Any N	M0
Stage IVB	Any T	Any N	M1

TABLE 4.5C Stage grouping for anaplastic thyroid carcinoma

Anaplastic (all cases are stage IV)			
Stage IVA	T1, T2, T3a	N0	M0
Stage IVB	T1, T2, T3a	N1	M0
	T3b, T4a, T4b	N0, N1	M0
Stage IVC	Any T	Any N	M1

Related classifications

The World Health Organization (WHO) has developed a series aimed at classification of tumours. The WHO International Classification of Diseases for Oncology (ICD-O) is a coding system for neoplasms by topography and morphology and for indicating behaviour (e.g. malignant, benign).[13] This coded nomenclature is identical in the morphology field for neoplasms to the Systemized Nomenclature of Medicine (SNOMED).[14] It is recommended that the WHO Classification of Tumours be used for classification and definition of tumour types and that the ICD-O code be used for storage and retrieval of data.

METHOD OF STAGING

The aim is to define in each patient all the factors relevant to the natural history and outcome of the relevant disease, thereby enabling a patient with cancer to be grouped with other similar cases. The sex and age of the patient, the duration and severity of symptoms and signs, and the presence and severity of intercurrent disease should all be documented.

CT and MRI are now established as the mainstay investigations in the pre-operative workup of patients with head and neck cancer. Not every patient requires a scan but they are useful in delineating the extent and size of the primary tumour, determining the presence (particularly when risk of occult nodes is >20%), number and position of cervical lymph nodes, searching for an occult primary and locating a synchronous primary or distant metastases (particularly in the chest). Appropriate screening for synchronous tumours and distant metastases is particularly important in advanced tumours. Several studies have suggested that a CT scan should be obtained in preference to a plain chest radiograph as this may miss significant lung disease.[15, 16]

Scans to evaluate the primary site should be performed **prior to biopsy** to avoid the effect of upstaging from the oedema caused by biopsy trauma.

Endoscopy and biopsy should be performed by a senior surgeon and in all cases by the head and neck surgeon responsible for any future procedure. For each tumour, this should include a description and diagrammatic representation, and preferably also photographic documentation. Routine panendoscopy (oesophagoscopy and bronchoscopy) is contentious. Proponents point out that these procedures require very little time, and may be performed easily during planned, direct laryngoscopy. A large meta-analysis found a small advantage to panendoscopy in detection of second primary tumours during analysis of multiple prospective studies.[17] Opponents point out that the appropriate use of symptom-directed investigations, in addition to routine chest imaging, have a similar detection rate compared with screening endoscopy and avoid unnecessary risk and expense in asymptomatic patients.[18]

Therefore, panendoscopy is only recommended for symptomatic patients or patients with primary tumours known to have a significant risk of a second (synchronous) primary tumour.

There is a natural desire to confer a stage on the tumour at presentation in the clinic and, certainly, after endoscopy. This should be avoided. It is better to rely on descriptive text to avoid changing the stage as more information becomes available. The cTNM classification based on examination, imaging, endoscopy and biopsy should be clearly documented in the case file only when all the above information is collated. The UICC book should be available in every theatre and clinic to assist in applying the **correct stage**.

Regional lymph nodes

The status of the regional lymph nodes in head and neck cancer is of such prognostic importance that the cervical nodes must be assessed for each patient and tumour. Lymph nodes are described as ipsilateral, bilateral, contralateral or midline; they may be single or multiple and are measured by size, number and anatomical location. Midline nodes are considered ipsilateral nodes, except for thyroid cancers. Direct extension of the primary tumour into lymph nodes is classified as lymph node metastasis.[1, 2]

Imaging for node detection and delineation is advisable if the neck is being scanned as part of the evaluation of the primary tumour, if there is a high chance of occult disease (e.g. supraglottic primary), to assess the extent of nodal disease, to define any deep nodal fixation, or if clinical detection is difficult because of a short, fat or previously irradiated neck.

Lymph nodes are now subdivided into specific anatomical sites and grouped into seven levels for ease of description (**Table 4.6**). The pattern of lymphatic drainage varies for different anatomical sites. However, the location of the lymph node metastases has prognostic significance. Survival is significantly worse when metastases involve lymph nodes beyond the first echelon of lymphatic drainage.[19] It is particularly poor for lymph nodes in the lower regions of the neck (i.e. level IV and level V (supraclavicular area)).

The UICC booklet alludes to the importance of levels in some sites, but does not present any definitions. The AJCC cancer staging manual gives a much more thorough account. It recommends that each N staging category be recorded to show, in addition to the established parameters, whether the nodes involved are in the upper (U) or lower (L) regions of the neck, depending on their location above or below the lower border of the thyroid cartilage.[1, 2]

The definitions of the N categories (**Table 4.7**) are the same for most head and neck sites (oral cavity, p16-negative pharyngeal carcinoma, larynx carcinoma, sinus carcinoma, salivary gland carcinoma). The UICC/AJCC eighth edition recognizes the importance of extranodal extension (previously called extracapsular spread). A patient with evidence of extranodal extension is automatically considered to be N3b reflecting their poorer prognosis. The presence of skin involvement or soft tissue invasion with deep fixation/tethering to underlying muscle or adjacent structures or clinical signs of nerve involvement are classified as clinical extranodal extension.

The latest edition has also introduced two separate staging systems (cTNM and pTNM) for neck metastases for human papilloma virus (p16-positive) oropharyngeal cancer (**Tables 4.8a and 4.8b**). Studies have shown a significant difference in outcome based on the number of pathologically positive lymph nodes, defining two categories: those with 1 to 4 (N1) versus 5 or more (N2) positive nodes. As the number of nodes can only be counted in the neck dissection specimen, a separate N system based on histological assessment of the neck dissection specimen

TABLE 4.6 Nomenclature of anatomical site of lymph node

Level I	Contains the submental and submandibular triangles bounded by the posterior belly of the digastric muscle, the hyoid bone inferiorly and the body of the mandible superiorly.
Level II	Contains the upper jugular lymph nodes and extends from the level of the hyoid bone inferiorly to the skull base superiorly.
Level III	Contains the middle jugular lymph nodes from the hyoid bone superiorly to the cricothyroid membrane inferiorly
Level IV	Contains the lower jugular lymph nodes from the cricothyroid membrane superiorly to the clavicle inferiorly
Level V	Contains the posterior triangle lymph nodes bounded by the anterior border of the trapezius posteriorly, the posterior border of the sternocleidomastoid muscle anteriorly and the clavicle inferiorly.
Level VI	Contains the anterior compartment lymph nodes from the hyoid bone superiorly to the suprasternal notch inferiorly. On each side the medial border of the carotid sheath forms the lateral border.
Level VII	Contains the lymph nodes inferior to the suprasternal notch in the upper mediastinum.

TABLE 4.7 Clinical N stage

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension without extranodal extension
N2	N2a – Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension without extrandodal extension N2b – Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension, without extranodal extension N2c – Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension, without extranodal extension
N3a	Metastasis in a lymph node more than 6 cm in greatest dimension without extranodal extension
N3b	Metastases in a single or multiple lymph nodes with clinical extranodal extension

TABLE 4.8a Clinical N stage for HPV (p16-positive) related oropharyngeal cancer

Nx	Regional lymph nodes cannot be asessed
N0	No regional lymph node metasases
N1	One or more ipsilatetal lymph nodes, none larger than 6 cm
N2	Contralateral or bilateral lymph nodes, none larger than 6 cm
N3	Lymph node(s) larger than 6 cm

TABLE 4.8b Pathologic N stage for HPV (p16-positive) related oropharyngeal cancer

Nx	Regional lymph nodes cannot be assessed
pN0	No regional lymph node metasases
pN1	Metastasis in 4 or fewer lymph nodes
pN2	Metastasis in more than 4 lymph nodes

TABLE 4.9 N staging for nasopharynx

N - Regional lymph nodes	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Unilateral metastasis, in cervical lymph node(s), and/or unilateral or bilateral metastasis in retropharyngeal lymph nodes, 6 cm or less in greatest dimension, above the caudal border of cricoid cartilage
N2	Bilateral metastasis in cervical lymph node(s), 6 cm or less in greatest dimension, above the caudal border of cricoid cartilage
N3	Metastasis in cervical lymph node(s) greater than 6 cm in dimension and/or extension below the caudal border of cricoid cartilage

Note: Midline nodes are considered ipsilateral nodes, and the supraclavicular triangle is defined by the lines joining the following three points – the superior margin of the clavicle at its sternal and acromial ends, and the point where the line of the neck meets the shoulder.

TABLE 4.10 N staging for thyroid carcinoma

N - Regional lymph nodes	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
N1a	Metastasis in Level VI (pretracheal, prelaryngeal, paralaryngeal) or upper/ superior mediastinal lymph nodes
N1b	Metastasis in other unilateral, bilateral or contralateral cervical (levels I–V) or retropharyngeal nodes

has been created (pTNM). Recognizing that lymph node size >6 cm does not have a prognostic role in surgically treated necks, no pN3 category exists.

The natural history and response to treatment of cervical nodal metastases from the nasopharynx are different, in terms of their impact on prognosis; thus, they justify a different N classification (**Table 4.9**). Regional lymph node metastases from well-differentiated thyroid cancer do not significantly affect the ultimate prognosis and, therefore, also warrant a unique system (**Table 4.10**).

Pathological classification (pTNM)

The pT, pN and pM categories correspond to the T, N and M categories. The extent of the tumour in terms of the location and level of the lymph nodes should be documented. In addition, the number of nodes that contain tumour and the presence or absence of extranodal extension of the tumour should be recorded. Histological examination of a selective neck dissection specimen usually includes ten or more lymph nodes; a radical or modified radical neck dissection specimen includes 15 or more lymph nodes.[1, 2]

Lip and oral cavity

The oral cavity extends from the skin-vermilion junction of the lips to the junction of the hard and soft palate above and to the line of the circumvallate papillae below. The anatomic sites and subsites are as follows:

- lip:
  - external upper lip (vermilion border)
  - external lower lip (vermilion border)
  - commissures
- oral cavity:
  - buccal mucosa
  - mucosa of the upper and lower lips
  - cheek mucosa
  - retro molar areas
  - buck-alveolar sulci, upper and lower (vestibule of mouth)
  - upper alveolus and gingiva (upper gum)
  - lower alveolus and gingiva (lower gum)
  - hard palate
  - tongue – dorsal surface and lateral borders anterior to vallate papillae (anterior two-thirds). inferior (ventral) surface
  - floor of mouth.

The eighth edition of the staging system recognizes the importance of depth of invasion and this is shown in **Table 4.11**.

(Superficial erosion alone of bone/tooth socket by gingival primary is not sufficient to classify a tumour as T4a).

TABLE 4.11 TNM clinical classification for lip and oral cavity

T – Primary tumour	
T1	Tumour 2 cm or less in greatest dimension and 5 mm or less depth of invasion
T2	Tumour 2 cm or less in greatest dimension and more than 5 mm but no more than 10 mm depth of invasion or tumour more than 2 cm but not more than 4 cm in greatest dimension and depth of invasion no more than 10 mm
T3	Tumour more than 4 cm in greatest dimension or more than 10 mm depth of invasion
T4a	Lip: tumour invades through cortical bone, inferior alveolar nerve, floor of mouth, or skin (chin or nose)
T4a	Oral cavity: tumour invades through cortical bone, into deep/ extrinsic muscle of tongue, maxillary sinus or skin of face.
T4b	Lip or oral cavity: tumour invades masticator space, pterygoid plates, or skull base, or encases internal carotid artery

Pharynx

The pharynx is divided into three regions: nasopharynx, oropharynx and hypopharynx. There have been significant changes in the eighth UICC/AJCC edition to reflect the very different biological and etiological differences between nasopharyngeal carcinoma, HPV-associated oropharyngeal carcinoma and non-HPV-associated oropharyngeal carcinoma, and hypopharyngeal cancer. The eighth edition staging manual has been divided into three separate entities – nasopharynx; HPV-associated (p16-positive) oropharyngeal cancer; and hypopharynx and non-HPV-associated (p16-negative) oropharyngeal carcinoma – to better reflect the variety of diseases arising in the pharynx.[1, 2]

Each region is subdivided into specific sites as summarized below.

OROPHARYNX

The oropharynx is the portion extending from the plane of the superior surface of the soft palate to the superior surface of the hyoid bone (or floor of the vallecula). It includes:

- anterior subsites (glosso-epiglottic area)
- base of tongue (posterior to the vallate papillae or posterior third)
- vallecula
- lateral subsites
- lateral wall
- tonsil
- tonsillar fossa
- tonsillar pillar
- posterior wall
- superior subsites
- inferior surface of soft palate
- uvula.

T categories in both p16-positive, HPV–associated oropharyngeal carcinoma and p16-negative, non-HPV-associated oropharyngeal carcinoma were equally valid from a prognostic standpoint and thus remain the same with two exceptions: the p16-positive classification includes no carcinoma in situ (Tis) (because of the non-aggressive pattern of invasive of p16-positive oropharyngeal carcinoma and the lack of a distinct basement membrane in the epithelium of Waldeyer's ring), and the T4b category has been removed from p16-positive oropharyngeal carcinoma (OPC) (because the survival curves of the T4a and T4b categories prove indistinguishable).[2] **Tables 4.12a** and **4.12b** summarize these changes.

TABLE 4.12a Oropharynx: p16-negative cancers or p16 immunohistochemistry not performed

T – Primary tumour	
T1	Tumour 2 cm or less in greatest dimension
T2	Tumour more than 2 cm but not more than 4 cm in greatest diameter
T3	Tumour more than 4 cm in greatest dimension or extension to lingual surface of the epiglottis
T4a	Tumour invades any of the following: larynx, deep extrinsic muscles of tongue genioglossus, hyoglossus, palatoglossus and styloglossus), medial pterygoid, mandible and hard palate
T4b	Tumour invades any of the following: lateral pterygoid muscle, pterygoid plates, lateral nasopharynx, skull base; or encases the carotid artery

TABLE 4.12b Oropharynx: p16-positive cancers

T – Primary tumour	
T1	Tumour 2 cm or less in greatest dimension
T2	Tumour more than 2 cm but not more than 4 cm in greatest diameter
T3	Tumour more than 4 cm in greatest dimension or extension to lingual surface of the epiglottis
T4	Tumour invades any of the following: larynx, deep extrinsic muscles of tongue (genioglossus, hyoglossus, palatoglossus and styloglossus), medial pterygoid, mandible and hard palate, lateral pterygoid muscle, pterygoid plates, lateral nasopharynx, skull base; or encases the carotid artery

NASOPHARYNX

The nasopharynx begins anteriorly at the posterior choana and extends along the plane of the airway to the level of the free border of the soft palate. It includes:

- superior wall
- posterior wall: from the level of the junction of the hard and soft palates to the superior wall
- lateral wall: including the fossa of Rosenmuller
- floor: superior surface of the soft palate.

The margin of the choanal orifices, including the posterior margin of the nasal septum is included with the nasal fossa.

There are two changes in nasopharynx T classifications relating to anatomic markers rather than depth of invasion (**Table 4.13**). The previous T4 criteria used synonymous terms 'masticator space' and 'infratemporal', which are now be replaced by a specific description of soft-tissue involvement to avoid ambiguity. In addition, adjacent muscle involvement (including medial pterygoid, lateral pterygoid and prevertebral muscles) are down-staged to T2 based on them having a more favourable outcome.[20]

HYPOPHARYNX

The hypopharynx is that portion of the pharynx extending from the plane of the superior border of the hyoid bone (or floor of the vallecula) to the plane corresponding to the lower border of the cricoid cartilage. It includes the piriform sinuses, the postcricoid area and the lateral and posterior pharyngeal walls. The current staging summary for hypopharynx is summarized in **Table 4.14**.

- Postcricoid area (pharyngo-oesophageal junction): extends from the level of the arytenoid cartilages and connecting folds to the inferior border of the cricoid cartilage, thus forming the anterior wall of the hypopharynx.

TABLE 4.13 Nasopharynx

T – Primary tumour	
T1	Tumour confined to nasopharynx, or extends to oropharynx and/or nasal cavity without parapharyngeal involvement
T2	Tumour with extension to parapharyngeal space and/or infiltration of the medial pterygoid, lateral pterygoid and/or prevertebral muscles.
T3	Tumour invades bony structures of skull base cervical vertebra, pterygoid structures and/or paranasal sinuses
T4	Tumour with intracranial extension and/or involvement of cranial nerves, hypopharynx, orbit, parotid gland and/or infiltration beyond the lateral surface of the lateral pterygoid muscle

Note: Parapharyngeal extension denotes postero-lateral infiltration of tumour beyond the pharyngo-basilar fascia.

TABLE 4.14 Hypopharynx

T – Primary tumour	
T1	Tumour limited to one subsite of hypopharynx and 2 cm or less in greatest dimension.
T2	Tumour invades more than one subsite of hypopharynx or an adjacent site, or measures 2–4 cm in greatest dimension, without fixation of hemilarynx.
T3	Tumour measures >4 cm in greatest dimension, or with fixation of hemilarynx or extension to oesophagus
T4a	Tumour invades any of the following: thyroid/cricoid cartilage, hyoid bone, thyroid gland, oesophagus, central compartment soft tissue
T4b	Tumour invades prevertebral fascia, encases carotid artery, or invades mediastinal structures

Note: Central compartment soft tissue includes prelaryngeal strap muscles and subcutaneous fat.

- Piriform sinus: extends from the pharyngo-epiglottic fold to the upper end of the oesophagus. It is bounded laterally by the thyroid cartilage and medially by the hypopharyngeal surface of the aryepiglottic fold and the arytenoid and cricoid cartilages.
- Posterior pharyngeal wall: extends from the superior level of the hyoid bone (or floor of the vallecula) to the level of the inferior border of the cricoid cartilage and from the apex of one pyriform sinus to the other.

Larynx

The anatomical sites and subsites are:

- supraglottis:
  - suprahyoid epiglottis (including tip, lingual [anterior], and laryngeal surfaces)
  - aryepiglottic fold, laryngeal aspect
  - arytenoid
  - infrahyoid epiglottis
  - ventricular bands (false cords)
- glottis:
  - vocal cords
  - anterior commissure
  - posterior commissure
- subglottis.

Tables 4.15–4.17 detail the T stages for the various laryngeal cancer sites.

TABLE 4.15 Supraglottis

T – Primary tumour	
T1	Tumour limited to one subsite of supraglottis with normal vocal cord mobility
T2	Tumour invades mucosa of more than one adjacent subsite of supraglottis or glottis or region outside the supraglottis (e.g. mucosa of base of tongue, vallecula, medial wall of pyriform sinus) without fixation of the larynx
T3	Tumour limited to larynx with vocal cord fixation and/or invades any of the following: postcricoid area, pre-epiglottic tissues, paraglottic space and/or with minor thyroid cartilage erosion (e.g. inner cortex)
T4a	Tumour invades through thyroid cartilage, and/or invades tissues beyond the larynx, e.g. trachea, soft tissues of the neck, including deep/extrinsic muscle of the tongue (genioglossus, hyoglossus, palatoglossus and styloglossus), strap muscles, thyroid and oesophagus
T4b	Tumour invades prevertebral space, mediastinal structures, or encases carotid artery

TABLE 4.16 Glottis

T – Primary tumour	
T1	Tumour limited to vocal cord (s) (may involve anterior or posterior commissure) with normal mobility. T1a – tumour limited to one vocal cord T1b – tumour involved both vocal cords
T2	Tumour extends to supraglottis and/or subglottis, and/or with impaired vocal cord mobility
T3	Tumour limited to larynx with vocal cord fixation and/or invades paraglottic space, and/or with minor thyroid cartilage erosion (inner cortex)
T4a	Tumour invades through thyroid cartilage or invades tissues beyond the larynx, e.g. trachea, soft tissues of neck including deep/extrinsic muscle of tongue (genioglossus, hyoglossus, palatoglossus and styloglossus), strap muscles, thyroid and oesophagus
T4b	Tumour invades prevertebral space, mediastinal structures, or encases carotid artery

TABLE 4.17 Subglottis

T – Primary tumour	
T1	Tumour limited to subglottis
T2	Tumour extends to vocal cord(s) with normal or impaired mobility
T3	Tumour limited to larynx with vocal cord fixation
T4a	Tumour invades through cricoid or thyroid cartilage and/or invades tissues beyond the larynx, e.g. trachea, soft tissues of neck including deep/extrinsic muscle of tongue (genioglossus, hyoglossus, palatoglossus, and styloglossus), strap muscles, thyroid, and oesophagus
T4b	Tumour invades prevertebral space, mediastinal structures, or encases carotid artery

Nasal cavity and paranasal sinuses

The anatomical sites and subsites are:

- nasal cavity:
  - septum
  - floor
  - lateral wall
  - vestibule
- maxillary sinus
- ethmoid sinus.

Other than the changes to the N stage (consistant with with oral caity, p16-negative oropharynx and larynx) there are no other alterations to sinus tumour stages (**Tables 4.18** and **4.19**).

Salivary glands

The classification applies only to carcinomas of the major salivary glands. Tumours arising in minor salivary glands (mucus-secreting glands in the lining membrane of the upper aerodigestive tract) should be staged according to their anatomic site of origin (e.g. lip). There should be histological confirmation of the disease. The anatomical sites and subsites are (**Table 4.20**):

- parotid gland
- submandibular gland
- sublingual gland.

TABLE 4.18 Maxillary sinus

T – Primary tumour	
T1	Tumour limited to the antral mucosa with no erosion or destruction of bone
T2	Tumour causing bone erosion or destruction, including extension into hard palate and/or middle nasal meatus, except extension to the posterior wall of maxillary sinus and pterygoid plates
T3	Tumour invades any of the following: bone of posterior wall of maxillary sinus, subcutaneous tissues, floor or medial wall of orbit, pterygoid fossa or ethmoid sinuses
T4a	Tumour invades any of the following: anterior orbital contents, skin of cheek, pterygoid plates, infratemporal fossa, cribriform plate and sphenoid or frontal sinus
T4b	Tumour invades any of the following: orbital apex, dura, brain, middle cranial fossa, cranial nerves other than maxillary division of trigeminal nerve, nasopharynx, clivus

TABLE 4.19 Nasal cavity and ethmoid sinus

T – Primary tumour	
T1	Tumour restricted to one subsite of nasal cavity or ethmoid sinus without bone erosion
T2	Tumour involves two subsites or extends to involve an adjacent site within the nasoethmoidal complex, with or without bony invasion
T3	Tumour extends to invade the medial wall or floor of the orbit, maxillary sinus, palate or cribriform plate
T4	Tumour invades any of the following: anterior orbital contents, skin of nose or cheek, minimal extension to anterior cranial fossa, pterygoid plates, sphenoid or frontal sinuses
T4b	Tumour invades any of the following: orbital apex, dura, brain, middle cranial fossa, cranial nerves other than maxillary division of trigeminal nerve, nasopharynx, clivus

TABLE 4.20 Salivary gland

T – Primary tumour	
T1	Tumour 2 cm or less in greatest dimension without extraparenchymal extension*
T2	Tumour more than 2 cm but no more than 4 cm in greatest dimension without extraparenchymal extension*
T3	Tumour more than 4 cm and/or tumour with extraparenchymal extension
T4a	Tumour invades skin, mandible, ear canal or facial nerve
T4b	Tumour invades base of skull, pterygoid plates or encases carotid artery

* Extraparenchymal extension is clinical or macroscopic evidence of invasion of skin, soft tissues or nerve, except those listed under T4a and T4b. Microscopic evidence alone does not constitute extraparenchymal extension for classification purposes.

TABLE 4.21 Thyroid gland

T – Primary tumour	
T1	Tumour 2 cm or less in greatest dimension, limited to the thyroid T1a – tumour 1 cm or less in greatest dimension, limited to the thyroid T1b – tumour more than 1 cm but not more than 2 cm in greatest dimension, limited to the thyroid
T2	Tumour more than 2 cm but not more than 4 cm in greatest dimension, limited to the thyroid
T3	Tumour more than 4 cm in greatest dimension, limited to the thyroid or any tumour with gross extrathyroid extension involving only the strap muscles (e.g. sternohyoid, sternothyroid or omohyoid muscles) T3a – tumour more than 4 cm in greatest dimension, limited to the thyroid T3b – tumour of any size with gross extrathyroidal extension invading strap muscles (sternohyoid, sternothyroid or omohyoid muscles)
T4a	Tumour extends beyond the thyroid capsule and invades any of the following: subcutaneous soft tissues, larynx, trachea, oesophagus, recurrent laryngeal nerve
T4b	Tumour invades prevertebral fascia, mediastinal vessels, or encases carotid artery
T4a*	(Anaplastic carcinoma only) – tumour (any size) limited to the thyroid
T4b*	(Anaplastic carcinoma only) – tumour (any size) extends beyond the thyroid capsule

Note: Multifocal tumours of all histological types should be designated (m) (the largest determines the classification).

* All anaplastic carcinomas are considered T4.

Thyroid gland

The four major histopathologic types are:

- papillary carcinoma (including those with follicular foci)
- follicular carcinoma (including Hürthle cell carcinoma)
- medullary carcinoma
- undifferentiated (anaplastic) carcinoma.

In the new UICC/AJCC staging system the definition of T3 has been revised for follicular and medullary carcinomas. In addition, the age for a poor prognosis has changed from 45 to 55 years. The current staging system is summarized in **Table 4.21**.

Unknown primary – cervical nodes

There should be histological confirmation of squamous cell carcinoma with lymph node metastases but without an identified primary carcinoma. It should be appreciated that this is a dynamic concept as eventual discovery of the primary site means that the carcinoma is no longer an unknown primary. Current recommended diagnostic methods include an early PET CT scan with targeted biopsies based on the findings. Transoral laser or robotic excision of the tonsil and tongue base mucosectomy are also recommended in cases which remain as an unkown primary. Histological methods should be used to identify EBV and HPV/p16-related tumours. If there is evidence of EBV, the nasopharyngeal classification is applied. If there is evidence of HPV and positive immunohistochemistry p16 overexpression, the p16-positive oropharyngeal classification is applied.[1, 2] One key change from previous versions of the TNM system is the elimination of the T0 category in sites other than the nasopharynx, HR-HPV–associated OPC, and salivary gland cancers (which can be identified by their unique histology). If no primary lesion can be identified, then the lymph node may have emanated from any mucosal site, so there is no rationale to support retaining the T0 designation outside of the virally associated cancers of the oropharynx and nasopharynx.

Skin carcinoma of the head and neck

This is now presented in a separate chapter in the eighth edition of the UICC/AJCC manuals.[1, 2] The classification aplies to cutaneous carcinaomas of the head and neck region excluding the eyelid (as an antomical site), Merkel cell carcinoma and malignant melanoma. The T stage is presented in **Table 4.22**, and N stage follows the same as nodal metastases from other sites of the head and neck. The following sites are recognized:

- lip
- external ear
- other and unspecified parts of the face
- scalp and neck.

TABLE 4.22 Head and neck skin cancer

T1	Tumour 2 cm or less in greatest dimension
T2	Tumour >2 cm and <4 cm in greatest dimension
T3	Tumour >4 cm in greatest dimension or minor bone erosion or perineural invasion or deep invasion*
T4a	Tumour with gross cortical bone/marrow extension
T4b	Tumour with skull base or axial skeleton invasion including foraminal involvement and/or vertebral foramen involvement to the epidural space

* Deep invasion is defined as invasion beyond the subcutaneous fat or >6 mm (as measured from the granular layer of adjacent normal epidermis to the base of the tumour), perineural invasion for T3 classification is defined as clinical or radiographic involvement of named nerves without foramen or skull base invasion or transgression.

Malignant melanoma of the upper aerodigestive tract

The classication in **Table 4.23** applies only to mucosal malignant melanomas of the head and neck region. The regional lymph nodes are staged according to the site in the upper aerodigestive tract of the tumour. As malignant melanoma are aggressive tumours, T1 and T2 are omitted as are stages I and II.

LIMITATIONS OF T STAGING

For most sites in the head and neck, emphasis is placed on tumour size. It is, however, well recognized that T stage alone is of limited prognostic significance in many head and neck carcinomas. It is a significant factor in the presence of nodes on presentation. Patients with larger tumours are more likely to have nodes than those with smaller tumours.[21] In carcinoma of the larynx, the poorer prognosis with increased T stage is explained by the increasing propensity to nodal metastases with larger tumours. If nodal metastases are removed as a confounding factor then T stage per se does not influence prognosis.[22]

Tumours of the larynx are classified according to the number of anatomical surfaces involved. This has led to several problems. For example, a large 3 cm tumour of the supraglottis may remain T1, whereas in the glottis this will almost certainly be a T3. This mitigates against supraglottic tumours in terms of outcome. In addition, depth of invasion is not measured, but is of prognostic and therapeutic importance. For example, a superficial tumour of the vocal cord mucosa would be T1a. The same tumour may be deeply infiltrating into the vocalis muscle and yet the stage will remain T1a.

TABLE 4.23 Malignant melanoma of the upper aerodigestive tract

TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
T3	Tumour limited to the epithelium and/or submucosa (mucosal disease)
T4a	Tumour invades deep soft tissue, cartilage, bone or overlying skin
T4b	Tumour invades any of the following: brain, dura, skull base, lower cranial nerves (IX, X, XI, XII), masticator space, carotid artery, prevertebral space, mediastinal structures

In the oral cavity and the oropharynx, the size of the tumour is not always easily measured. There is little difficulty in defining a T1 or T4 tumour, but problems can occur when the tumour measures between 1.5 and 3 cm. Furthermore, increasing severity with a T4 tumour is reflected in deep invasion into muscle, bone or adjacent structures. There is then a reliance on the predictive power of radiographic modalities including CT and MRI. The depth of invasion of lesions of the floor of the mouth has been shown to be of prognostic significance and this is similarly difficult to assess by either clinical or radiographic means.[23]

Tumours of the hypopharynx are classified in terms of both their size and anatomical extent. The anatomical boundaries of the hypopharynx have been contentious in the past and it is occasionally difficult to be certain of the exact origin of some of the larger tumours. The dual listing of the aryepiglottic fold in both the supraglottis and hypopharynx sites invokes a problem in trying to classify the site of origin in some situations.

LIMITATIONS OF N STAGING

The reliability of clinical examination of nodes is contentious with studies showing that observers disagree on their presence.[23] Furthermore, palpable nodes do not always harbour tumour. During clinical examination, the size of the node should be measured with callipers, and allowance made for the intervening soft tissues. There is considerable inter- and intra-observer error in estimating the size of the node by palpation alone without a measuring device.[24] Most masses over the size of 3 cm in diameter are not single nodes, but will represent confluent nodes or tumour in the soft tissue compartments of the neck.

One of the main criticisms over many years was the failure of the TNM system to provide a description of the level of nodal involvement. Various studies have confirmed the importance of this parameter[25] and it is now included in the current classification (engaging the Memorial Sloan-Kettering system of lymph node levels).[1, 2]

LIMITATIONS OF STAGE GROUPING

There are now seven stages for head and neck cancers arising at mucosal sites (0, I, II, III, IVa, IVb, IVc) and six stages for salivary gland cancers (I, II, III, IVa, IVb, IVc). Differentiated thyroid cancers also have six stages (I, II, III, IVa, IVb, IVc) with undifferentiated (anaplastic) cancers having three, as all cases are stage IV (IVa, IVb, IVc). Many authorities have concluded that problems exist with the current staging system.[25–28] One of the main criticisms is that the size of some groups defined by the combinations of the TNM classifications is small, preventing accurate prediction from previous experience.

Groome et al.[29] identified four criteria that a stage-grouping scheme should meet:

1. The subgroups defined by the T, N and M that make up a given group within a stage grouping scheme should have similar survival rates (hazard consistency).
2. The survival rates should differ among the groups (hazard discrimination).
3. The prediction of cure should be high (outcome prediction).
4. The distribution of patients across the groups should be balanced (thereby maximizing statistical power in each group).

Compelling arguments have been advanced to show that alternative groupings of the same T, N and M categories will result in an improved system.

The T and N integer score (TANIS) combines the integers of the T and N to create a new score. Thus, a T1N0 would be a TANIS 1, T2N2 would be a TANIS 4, and so on. First reported by Jones et al.,[28] this is an easy to use system evaluated primarily for cancers of the oral cavity and oropharynx. It treats T and N as equivalent with respect to survival. Many authors have studied this system and recommended grouping several TANIS scores to improve hazard discrimination. In their initial report, Jones et al. found little statistical difference between groups 1–3 and 5–7. They recommended pooling TANIS scores 1–3 together as TANIS 1, 4 as TANIS 2 and 5–7 as TANIS 3. Others have tried different groupings based on the TANIS system.[29, 30]

The advantages of the TANIS score are its ease of application, ability to define a reasonable number of groups and ability to be applied retrospectively if the TNM score is known. The main disadvantage is that the concept of T and N equivalence does not hold true. Many studies have confirmed the more significant impact of N status over T status. For example, a T2N0 carcinoma does not have the same survival as a T1N1 at any site although both of these would be categorized TANIS 2. The TANIS system does not account for M1 disease, although most would agree that any M1 would automatically put the patient in the highest TANIS group. It is also apparent that by pooling groups, because there is little difference in survival between them (attempting to improve hazard discrimination), there is an implicit trade-off with hazard consistency.

Others have also tried to improve on the current stage grouping and TANIS system with subtle variations,[26, 31, 32] all claiming that their system is an improvement on any other. It seems that excellent systems have been devised that may improve predictive power, hazard consistency, hazard discrimination and balance over the current UICC/AJCC T, N and M stage grouping system. Lydiatt et al.[33] provide a review of these. They observe that one of the main disadvantages is that the systems are not intuitive and would require a chart for most clinicians to stage their patients. In most publications, analyses comparing the authors' systems with other systems, including the UICC/AJCC, are flawed because the new system under consideration was not externally validated on an independent dataset. Therefore, because the system was created from the dataset, it would naturally perform well. The true test is whether the results from an independent dataset would yield similar results.

The five major sites of the head and neck (oral cavity, oropharynx, larynx, hypopharynx and paranasal sinuses)

share the same system. Arguably, they should be independent of each other. One advantage of an independent system is better groupings within each site. Different systems are in use for the nasopharynx and thyroid, which are sufficiently different with respect to risk factors, behaviour and treatment. In their rebuttal of these views, the AJCC Task Force maintains the opinion that independent systems would create problems for clinicians and investigators not remembering which group was staged by which system. They are of the view that any new system should be comprehensive and easily applicable to all the major sites.[33]

FUTURE RESEARCH

- Definitions of TNM categories may be altered or expanded for clinical or research purposes as long as the basic definitions are recorded and not changed. Changes in the TNM classification should and will only occur, based on the appropriate collection, presentation and analysis of data, in the forum of the UICC and AJCC.
- The TNM system embraces the concept of orderly description of disease with increasing size and extent. While fallible, it is founded on sound principles and relates the combined experience and data from many surgeons and centres. Many of the shortcomings in the system represent the complexity of the disease of head and neck cancer.
- Future versions of the staging system may well incorporate nomograms and personalized approaches; but, for now, the eighth edition strikes a balance between a personalized, complex system and a more general, simpler one that maintains the user-friendliness and worldwide acceptability of the traditional TNM staging paradigm.

KEY POINTS

- Staging of head and neck cancer is a system designed to express the relative severity, or extent, of the disease. It is meant to facilitate an estimation of prognosis and provide useful information for treatment decisions.
- Classification of the anatomical extent of head and neck cancer as determined clinically and histopathologically is called the TNM system.
- Radiological investigations to evaluate the primary site should be performed prior to biopsy to avoid the effect of upstaging from the oedema caused by biopsy trauma.
- The age and sex of the patient, the duration and severity of symptoms and signs, and the presence and severity of intercurrent disease should all be documented. The literature does suggest that symptom severity[34] and comorbidity[35] have a significant impact on outcomes. It is therefore recommended that these data be recorded and this additional information can be used as part of the prognostic grid.
- Assessment by endoscopy and biopsy should be performed by a senior surgeon and in all cases by the head and neck surgeon responsible for any future procedure.
- The clinical (pre-treatment) classification (cTNM) based on examination, imaging, endoscopy and biopsy should be clearly documented in the case file only when all the information is collated.
- Individual TNM classifications should be assembled into four stage groups (Stages I to IV), each with similar survival outcomes.
- The UICC book[1, 2] should be available in every theatre, MDT meeting and clinic to assist in applying the correct stage.

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CHAPTER 5

THE CHANGING FACE OF CANCER INFORMATION

Richard Wight

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SEARCH STRATEGY

Data in this chapter may be updated by a PubMed search using the web links given within the reference list.

INTRODUCTION

This chapter describes principles to be followed in capturing high quality cancer data. The principles are transferable to other aspects of otolaryngology. A description is provided of the changing nature of cancer information collection and collation with the National Cancer Outcomes and Services Data Set, unification of cancer registration in England and national radiotherapy and chemotherapy data collection, as well as the National Comparative Audit in Head and Neck Cancer (Data for Head and Neck Oncology, DAHNO).

WHAT ARE DATA?

Data are a collection of directly observed facts, and the storage of these facts in a standardized format and content comprise a database.

For standardization of content, data gathering requires an underlying 'skeleton' of items: a data set. The items need to have defined meaning, standard terminology should be used, and choice of fields should have a consistent coding structure. Use of free text should be avoided. The items are the building blocks from which the construction of information can then subsequently occur. If the data set has been correctly defined and is fit for the purpose, then it should contain all the items needed for the outputs proposed without the need to resort to additional data capture.

WHY COLLECT CANCER DATA?

All clinicians managing patients with cancer have a responsibility to assess the quality of the care they provide.[1] This is reflected in the impact or consequences of the management and treatments they apply to individuals or groups of patients. In order to discharge this responsibility, the prospective collection of data on each patient to derive simple outcomes is a minimum requirement. Potential outcomes are: knowledge of the range of malignancies treated; stage distribution; the types of treatment provided; complications of treatment; survival; and quality of life measures.

Clinicians seek to provide for their patients a prognosis for their disease. This is affected by tumour-specific factors (e.g. stage,[2] pathological features), host factors (e.g. performance status and comorbidities) and environmental factors (e.g. access to services and the availability of treatments).[3] Traditionally, prognosis has been based on anecdote and the 'best of class from the literature' but by routine data capture it can (if sufficient

numbers are obtained) be converted into a true local focus. Customization for an individual's personal circumstances is becoming increasingly important as illustrated by the impact of comorbidities. These are the additional burdens of other diseases present at the time of diagnosis of the index cancer. A series of standardized indexes are available, with the adult comorbidity evaluation (ACE-27) having significant prognostic value.[4]

WHY A MINIMUM DATA SET?

Applying the principle of a minimum data set is based on the fact that the smaller the volume of items the greater the speed of entry, the higher the accuracy and the greater the likelihood of compliance in usage. This has to be balanced against the requirements of components to deliver the necessary outcomes, without additional data entry at a later stage. To produce a minimum data set, each item proposed should be critically examined both in its definition and by it having a defined purpose for inclusion, and these should be reviewed in the light of any piloting.

An ongoing recording of current status in relation to the absence or presence of the index cancer is needed with capture of recurrence or metastasis events, to allow for the censoring of records ultimately in certain types of survival analysis. Creation of a supporting data manual providing an expanded description of each item, its purpose in inclusion and any associated codes and classifications, is of value to support staff, institutions and software writers.

HOW TO DEVELOP CANCER DATA COLLECTION

In commencing an initiative to record cancer data, the goal has to be to collect data at the point of contact with the patient along their care journey (real or near real time data capture). This reduces error and increases likely compliance from health professionals. Duplication is reduced and the data collection process can deliver added value by-products such as referral or discharge letters.

The key steps are shown in **Figure 5.1**. Some items will be derived. For example, it is better to record date of birth and date of an event, then calculate the age at the event subsequently, than it is to enter the age as a free field item. The latter is prone to error, as well as being repetitive if a series of events require age as a factor.

At introduction, for a data set to be successfully collected requires a change in culture by all contributory professionals. A sense of ownership is needed as well as carefully focused drives to ensure data quality on a recurring basis. It is appropriate to validate the data, to ensure all relevant cases have been captured within the geographical target area and particularly where patient care crosses organizations the full record has been collected. Useful sources for cross comparison are multi disciplinary (MDT) meeting lists, pathology, and cytology records. The Office for National Cancer Registration and Analysis service collate the small number of additional death certificate-only registrations.

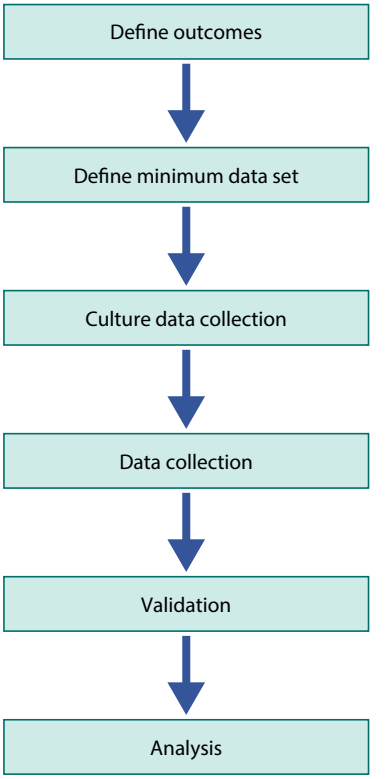

Figure 5.1 The key stages in developing cancer data collection.

When appropriate, data analysis can then occur and this is mostly likely to fail if significant gaps in the data are evident. Only with high quality data can relevant and useful information be assembled.

The data set should not be seen as fixed, but its items should be reviewed on a regular basis both to encompass any changes and confirm that their continued collection remains relevant and of value.

STRUCTURE OF A COMPUTERIZED DATABASE

Each subject on the database requires a unique identifier, and a record of registration is created. In England the mandated identifier is the NHS number. Diagnosis of cancer produces a care spell or event, to which is then tagged each recurrence or metastasis and each treatment plan and treatment. An additional new primary creates a new care spell. A relational database tree is thus constructed.

In selecting database software to support this, a number of factors should be considered:

- local familiarity, including the ability to write in the software to amend for item changes
- flexibility to deliver changes in relationship between events and to support different system packages
- ability to link with other host institutional systems for automated data capture (e.g. link to patient administration systems)
- ability to export data in a number of formats is also of value.

CONFIDENTIALITY – SECURE DATA

Patients expect that information about them will be held in confidence by the health professionals who care for them. Where information is stored in computerized or paper records, it must be effectively protected against improper disclosure at all times.

For the majority of audit purposes anonymized data will meet requirements. If data cannot be used in an anonymized format then permission should be sought from the patient.

Legislation controls confidential information disclosures (Section 251 of the NHS Act 2006) which allow sharing of confidential information in the 'public interest.' It sets a high threshold before the duty of confidentiality can be set aside for the purposes of audit not directly associated with care.[5]

CODING CLASSIFICATIONS

Standardized nomenclature is essential to allow assimilation of data from different units and specialities, and should wherever possible be recognized internationally (e.g. International Classification of Disease (ICD)-10); nationally (e.g. Office for Population Censuses and Surveys (OPCS)-4 operation codes, Systematized Nomenclature of Medicine – Clinical Terms (SNOMED CT)); or national professional (e.g. BAHNO extension codes). Locally derived codes should be avoided wherever possible. To illustrate coding classification structures, some are described briefly here.

ICD-10 tumour site codes

The classification of neoplasms is broken down into categories based on their point of origin and behaviour.[6] Sites for malignant neoplasms are prefixed by C, whilst sites for *in situ* and benign neoplasms are prefixed by D, but grouped into much broader categories (see **Box 5.1**).

For each anatomical site the initial three alphanumeric code is supplemented by a decimal point and an additional digit to identify subsite 0 to 7, or an overlapping site 8 (unless specifically indexed), or unspecified subsite 9 (see **Box 5.2**).

BOX 5.1 ICD-10 tumour site codes (benign and malignant)

C00–C75	Covers specified primary sites (but excludes lymphoid, haematopoietic and related tissues)
C76–C80	Covers ill-defined, secondary and unspecified sites
C81–C96	Malignant neoplasms of lymphoid, haematopoietic and related tissues
C97	Malignant neoplasms of multiple independent primary sites
DOO–DO9	Relates to *in situ* neoplasms
D10–D36	Relates to benign neoplasms
D37–D48	Relates to neoplasms of uncertain or unknown behaviour

BOX 5.2 ICD-10 tumour site codes for the tonsil

CO9	Malignant neoplasm of tonsil (excludes lingual tonsil CO2.4, pharyngeal tonsil C11.1)
CO9.0	Tonsillar fossa
CO9.1	Tonsillar pillar (anterior and posterior)
CO9.8	Overlapping lesion of tonsil (i.e. involves pillar and fossa and not clear which is site of origin)
CO9.9	Tonsil unspecified (i.e. subsite not stated or known)

ICD-O-3 – morphology codes

ICD-10 includes a copy of this coding system to allow it to be used in conjunction with the above site codes, to identify histological type.[7] Morphology codes are prefixed by M. Some histological types of neoplasm are specific to certain sites or types of tissue and C and D site codes are shown after these. For example, M93103 ameloblastoma malignant (C41.0, C41.1) identifies that the morphology only relates to tumours occurring in the maxilla and mandible.

Four identity digits for the histological type of neoplasm, and then a one-digit behaviour code follow:

0 benign
1 uncertain benign or malignant
2 carcinoma *in situ*
3 malignant or primary site
6 malignant metastatic, or secondary site

This system as it applies to squamous carcinoma is illustrated in **Box 5.3**

The morphology section of the Systematized Nomenclature of Medicine – Clinical Terms (SNOMED CT)[8] is similar to ICD-O-3 , but it gives a broader description of pathological terminology to aid coding.

OPCS operation codes

The basic structure of the classification comprises anatomically based chapters, each of which is given an alphabetical code.[9] The next two digits describe the operation group, based on the largest operation first, descending to the smallest, followed by a decimal point and a fourth digit to identify the procedure itself. If the procedure specified does not match these categories, then provided the procedure is recorded a .8 can be added, and where unspecified a .9 can be added. Within the classification, certain codes do encompass multiple procedures, but otherwise the operation needs to be coded from its component parts (e.g. having defined the primary resection procedure, separate codes for type of flap and its site of harvest need to be added). Operations on the salivary glands are illustrated in **Box 5.4**.

BOX 5.3 ICD-O-3 morphology codes for squamous carcinoma

M8070/2	Squamous cell carcinoma *in situ*
M8070/3	Squamous cell carcinoma (not otherwise specified)
M8070/6	Squamous cell carcinoma metastatic (i.e. in a node with an unknown primary)

BOX 5.4 OPCS operation and procedure codes: salivary gland procedures

F44	Excision of salivary gland
F44.1	Total excision of parotid gland
F44.2	Partial excision of parotid gland
F44.3	Excision of parotid gland (not elsewhere classified)
F44.4	Excision of submandibular gland
F44.5	Excision of sublingual gland
F44.8	Other specified
F44.9	Unspecified

NATIONAL CANCER REGISTRATION

Increasingly, cancer data capture is based on national initiatives. In Europe this has focused on registry-based systems,[10] and in the United States registry databases feed to the National Cancer Database.[11]

The Cancer Reform Strategy (2007)[12] identified better information as one of the key drivers to achieve the goal that cancer services in the UK should be amongst the best in the world. The subsequent *Improving Outcomes: A Strategy for Cancer* (January 2011) further supported this concept.[13]

In the UK, 2013 saw completion of the deployment of a National Cancer Registration System (NCRS),[14] in which the individual English cancer registries have been unified into a single online system. Regional registries have become eight regional cancer registration offices. There are also three cancer registries in Wales,[15] Scotland[16] and Northern Ireland.[17] NCRS receives data from a variety of sources including death certification from the Office for National Statistics (ONS) and direct feeds from pathology systems, MDTs and national audits, as well as treatment data on radiotherapy from the National Radiotherapy Data Set (RTDS) and on chemotherapy from the Systemic Anti-Cancer Therapy (SACT) data set. NCRAS is overseen by Public Health England.

CANCER OUTCOMES AND SERVICES DATA SET

In January 2013 the Cancer Outcomes and Services Data Set (COSD) replaced the previous National Cancer Dataset as the new NHS national requirement for reporting cancer in England. It incorporates a revised generic Cancer Registration Data Set (CRDS) and additional clinical and pathology site-specific data items relevant to different tumour types including items specific to head and neck.[18] The latest version of COSD can be found at http://content.digital.nhs.uk/isce/publication/dcb1521.[19]

COSD items are required to be submitted electronically by English NHS trusts to the National Cancer Registration and Analysis Service (NCRAS) on a monthly basis.[20]

COSD is aligned with, and shares data items with, other related data sets such as the National Cancer Waiting Times Monitoring Data Set (NCWTMDS),[21] the RTDS, the SACT data set, the Diagnostic Imaging Dataset (DID)[22] and the national clinical audits.

From 1 April 2009, all facilities providing radiotherapy services in England have been required to return the RTDS, which includes treatments delivered and aspects of fractionation.[23]

Submission of the SACT data set, which covers chemotherapy treatment for all solid tumour and haematological malignancies, including those in clinical trials for all patients receiving cancer chemotherapy in or funded by the NHS in England, commenced in 2013.[24]

NATIONAL CANCER DATA REPOSITORY AND THE FUTURE OF CANCER INFORMATION

By taking multiple data sources such as NCRAS, hospital episode statistics (HES), ONS death data and audit data, and linking these by NHS number, a comprehensive bank of data has been created in the National Cancer Data Repository,[25] which will be of value for national information reporting and analysis, as well as acting as a high quality clinical database for researchers enabling studies of treatments where it is impracticable to carry out randomized controlled studies.

NATIONAL CANCER INTELLIGENCE NETWORK HEAD AND NECK INFORMATION HUB

The National Cancer Intelligence Network (NCIN)[26] is a UK-wide initiative, working to drive improvements in standards of cancer care and clinical outcomes by improving and using the information collected about cancer patients for analysis, publication and research.

The NCIN Head and Neck Cancer Hub provides data and intelligence on head and neck cancers in England.[27] It is aimed at a wide range of professionals working in the field, including NHS providers, commissioners, cancer networks, charities and clinicians. Detailed reports are available on geographic variation, the impact of travel times and changes in head and neck surgery. It also provides information and links for patients and the general public who wish to understand more about head and neck cancers, including data sheet information about incidence and mortality, and past and current trends.

NATIONAL COMPARATIVE AUDIT IN HEAD AND NECK CANCER IN ENGLAND AND WALES

In England and Wales a partnership between the British Association of Head and Neck Oncologists (BAHNO) and the Health and Social Care Information Centre South East Knowledge and Intelligence Team, sponsored by the Healthcare Quality Improvement Partnership (HQIP), delivered Data for Head and Neck Oncology (DAHNO),[28] a national comparative audit for head and neck cancer.

Core issues addressed in the audit were:

- delivery of appropriate primary treatment (including adjuvant therapy) in management of head and neck cancer by an MDT, and delivery of care to agreed standards
- to assess in more detail, care provided by specialist nurses, dieticians and speech and language therapists.

The audit compared reported delivery against clinical standards produced by BAHNO as well as making peer-to-peer comparisons between organizations, MDTs and cancer networks.

The project defined outcomes deliverable by items from the core and head and neck specific COSD data set. The first annual report looking at outcomes related to patients with laryngeal and oral cavity cancer was published in March 2006. Subsequent reports extended across a broad range of anatomic sites, including the pharynx, major salivary glands and most recently the nose and nasal sinuses. More than 54 000 cases have been collated and the tenth annual report, published in September 2015[29] had universal coverage from all hospitals delivering head and neck cancer care in England and Wales.

In a subsequent partnership between BAHNO and a charity Saving Faces, a new national comparative audit in head and neck cancer (HANA) is in development.[30]

EVOLVING SURGEON-SPECIFIC DATA

Publishing of outcomes data by named consultant is well established in a number of countries around the world, particularly in North America. This has now extended to head and neck cancer surgeons in England.

In December 2012, the NHS Commissioning Board (from April 2013 NHS England) published its planning guidance for 2013/14, *Everyone Counts: Planning for patients 2013/14*,[31] commencing a process in which specialist bodies (in conjunction with NHS Choices) were required to publish activity, clinical quality measures and survival rates from 10 national clinical audits, which included head and neck cancer. The aim of using consultant-level data was to drive up quality, facilitate patient choice and support the requirements of professional revalidation. It also aimed to reassure the public that clinical practice is being actively monitored, and that the overall standard of care is very high. Under the Clinical Outcomes Publication (COP), an NHS England initiative, commissioned and managed by HQIP information on aspects of head and neck cancer, including mortality and surgeons' activity, was published openly for the first time at individual consultant surgeon level on NHS choices in 2013.[32] This demonstrated the commitment of BAHNO and the head and neck community to the transparency agenda, and the latest report is now available.[33]

BEST CLINICAL PRACTICE

✓ The measures for improving outcomes in head and neck cancer issued by the National Institute for Clinical Excellence (NICE) support the proposition that clinicians should routinely collect data to assess care.[34]

FUTURE RESEARCH

➤ The relative rarity of head and neck cancer means that, in order to assess and compare results from different treatment regimes and practice and reach statistical significance, it requires comprehensive data collection from as many units as possible across the UK. The goal has to be to achieve high levels of completeness on a regular and systematic basis.

KEY POINTS

- Data gathering requires an underlying 'skeleton' of items – a data set. The items need to have defined meaning, standard terminology should be used, and choice fields should have a consistent coding structure.
- All clinicians managing cancer patients have a responsibility to assess the quality of the care they provide. In order to discharge this duty, the prospective collection of data on each patient to derive simple outcomes is a minimum requirement.
- In commencing an initiative to record cancer data, the goal has to be to collect data at the point of contact with the patient along their care journey.
- Patients have a right to expect that information about them will be held in confidence by the health professionals who care for them.
- The National Cancer Outcomes and Services Data Set (COSD) for England was introduced in January 2013.

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CHAPTER 6

INTRODUCING MOLECULAR BIOLOGY OF HEAD AND NECK CANCER

Nikolina Vlatković and Mark T. Boyd

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SEARCH STRATEGY

The data in this chapter are based on a PubMed searches including the following Medical Subject Headings (MeSH) and keywords: head and neck neoplasms, carcinoma, squamous cell, molecular biology, genome, papillomaviridae and tumour virus infections.

The rule is, jam to-morrow and jam yesterday—but never jam to-day.

Lewis Carroll, *Through the Looking-Glass, and What Alice Found There*

BACKGROUND – INTRODUCTION TO MOLECULAR BIOLOGY

Cancer is a genetic disease. Molecular biology permits the analysis of genes and their function and offers the chance to understand the information we can read in the genome and to predict the consequences for biological and pathological processes.

What is molecular biology? More importantly, why should a clinician or surgeon be interested in it – indeed, should they be at all? The *Oxford English Dictionary* defines molecular biology as 'the branch of science concerned with the formation, organization, and activity of macromolecules essential to life (nucleic acids, proteins, etc.)'. Many diseases arise from errors in biochemical processes (diabetes, for example), and many of these are due to genetic changes or inherited polymorphisms or mutations (cystic fibrosis, for example). (Polymorphism is a common (>1%) variant allele, cf. mutation or mutant allele: a rare <1% or acquired somatic change in nucleic sequence, usually but not always in the coding sequence of a gene.) Moreover, many of the modern treatments for disease, such as some of the monoclonal antibody drugs (mAbs), such as cetuximab (Erbitux®), nivolumab (OPDIVO®) and adalimumab (HUMIRA®) used to treat diseases including cancer and rheumatoid arthritis,[1–3] have been generated using molecular biological techniques (DNA cloning and sequencing). Thus it seems obvious that to understand disease, and to understand many of the treatment options, requires some level of understanding of molecular biology.

If we had tried to write this chapter only 10 years ago, there would have been some amazing technology and some wonderful insights into the nature of the disease, but whilst molecular biology promised much, it had yet to deliver substantially in the clinic, hence the quotation from *Alice in Wonderland* that starts this chapter. Happily that situation is no longer the case, and molecular biology has enabled the development of novel treatments for many types of cancer that are having a dramatic impact on patients, albeit often coming with a heavy financial burden. In the UK, in 2015–16, six of the seven most expensive hospital prescriptions for NICE-approved drugs were produced using molecular biological techniques (either as mAbs or recombinant peptides) and cost the system approximately £1.3 billion. This also highlights the fact that the rate of change is now overwhelming. At the time of writing there are 67 US Food and Drug Administration (FDA)-approved mAbs and in the region of 400 at various stages of testing and development.

Molecular biology is impacting on many aspects of clinical medicine, but for several reasons it has a special relevance to oncology. Essentially this is because cancer is fundamentally a genetic disease, or perhaps it is better to say that cancer is a disease of our genes. No gene

mutations = no cancer, even when a virus is involved as a causative agent! So the use of the technology of molecular biology to analyze tumours has followed hot foot upon the advances in molecular technologies. In the middle of the second decade of the twenty-first century, technology provides us with the potential essentially to identify all of the mutated genes in a biopsy of tissue from an individual tumour site. (There are even tests that reveal their answers in hours, such as One-Step Nucleic Acid Amplification (OSNA), permitting peri-operative information such as nodal involvement to be provided to surgeons.)[4]

From this it follows that if we could understand the function of the mutated genes and how alterations of these impacted on cellular processes, then we could predict the behaviour of the tumour both in terms of its growth and its progression and even how it will respond to a given therapy. However, tumours arise in an individual body, and so the same genetic information, that of the host or patient, should also be able to inform us about the way the patient's body will react to the tumour. So, the potential exists to have a high-resolution image of both the tumour and the body in which it arises, and thus potentially to understand how the tumour will behave, and how the body will respond to that. This particular level of understanding has not yet been reached, but it is clear that the potential is real and seems likely to be substantially achieved sometime during the next decade or so.

In many healthcare systems, there are other limitations to exploiting state-of-the-art technologies, but even for those without access to the very latest technology it remains possible, and increasingly clinically important, to obtain information from molecular analyses that are already being used as part of the routine diagnosis and stratification of patients, with immunohistochemistry for p16 being a good example of a biomarker with particular significance in oropharyngeal squamous cell carcinomas (OPSCC).[5–7]

The aim of this chapter is to review some of the available knowledge and to try to explain the ideas behind our molecular understanding of the basis of cancer, which is also the basis for understanding new diagnostic and therapeutic approaches

We will first briefly mention the technology, then review in more detail the fundamental process of carcinogenesis as it is understood at a molecular level, including how mutations and alterations arise. (For a more detailed treatise on the molecular basis of cancer, both editions of *The Biology of Cancer* by Robert A. Weinberg are highly recommended.)[8, 9] We will then summarize some of the molecular pathways that have been most commonly identified to be altered in head and neck cancers. This will entail a brief discussion of some of the critical tumour suppressors and oncogene networks that are known to harbour mutations and we will briefly describe the normal function of these and the consequences of the observed tumour alterations. Then we will briefly discuss some of the applications of this information and lastly the challenges and limitations facing the effective use of this information for patient benefit.

MOLECULAR TECHNOLOGY

As a practical subject, molecular biology was born following the discovery of restriction endonucleases, enzymes that could cut double stranded DNA at defined sites by recognizing specific sequences in the DNA.[10] The next major developments included the invention of a means to sequence DNA (most often by the di-deoxy sequencing method invented by Fred Sanger)[11] and a process to amplify specific sequences of DNA (the polymerase chain reaction invented by Carey Mullis).[12] However, our understanding of head and neck cancer has been revolutionized by so-called next-generation sequencing of whole genomes and exomes. These technologies vary and have been developed in parallel by several companies. The two most commonly used technologies, Illumina/Solexa and SOLiD, have been used to generate enormous quantities of data. Both approaches enable a high depth of sequence coverage, which is particularly important for studies of cancer since the tumour biopsy may contain a mixture of normal and tumour tissues and, moreover, due to the heterogeneity of cancers, there may be many clones with some common and some distinct mutations. In addition to high depth of coverage sequence analysis, it is now possible to examine the transcriptome (the mRNA products of the genes being actively transcribed) in greater detail and more quantitatively using RNA-Seq.[13] In addition, the application of RNAscope™ is beginning to impact on the analysis of fixed tissue biopsy sections. In particular, this has been used for the detection of human papilloma virus (HPV) gene expression.[14, 15] Much of what we now know about head and neck cancer molecular biology has been generated in the last few years by next-generation sequencing, as will become clear later.

THE MOLECULAR BIOLOGY OF HEAD AND NECK CANCER

Introduction to cancer molecular biology

Cancer is essentially a disease caused by genetic modifications of the information content of the genome such as base mutations and translocations or other chromosomal rearrangements. Indirect effects resulting in altered gene regulation through epigenetic alterations that affect chromatin structure and gene expression may also occur and are important factors in the development of cancer. In all cases, the carcinogenic events typically affect the function of a subset of critical genes regulating processes such as cell survival, proliferation, invasiveness and interactions with the host (the hallmarks of cancer, see **Figure 6.1**). Mutations may be inherited or acquired as somatic mutations (see **Figure 6.2**). However, unlike cancers of the colon and breast, there are no common inherited cancer syndromes that lead to head and neck cancer. Whilst individuals with the rare autosomal recessive disease Fanconi anaemia that affects approximately 3/1 000 000 individuals worldwide[16] do display an increased risk of developing cancers of the head and neck,[17] none of the genes

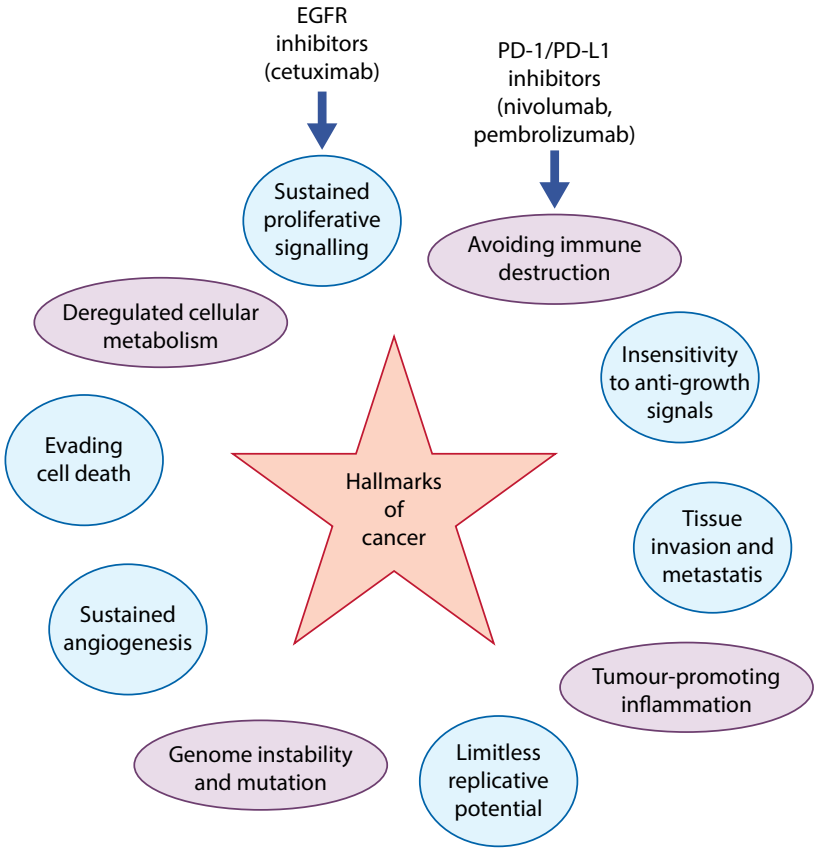
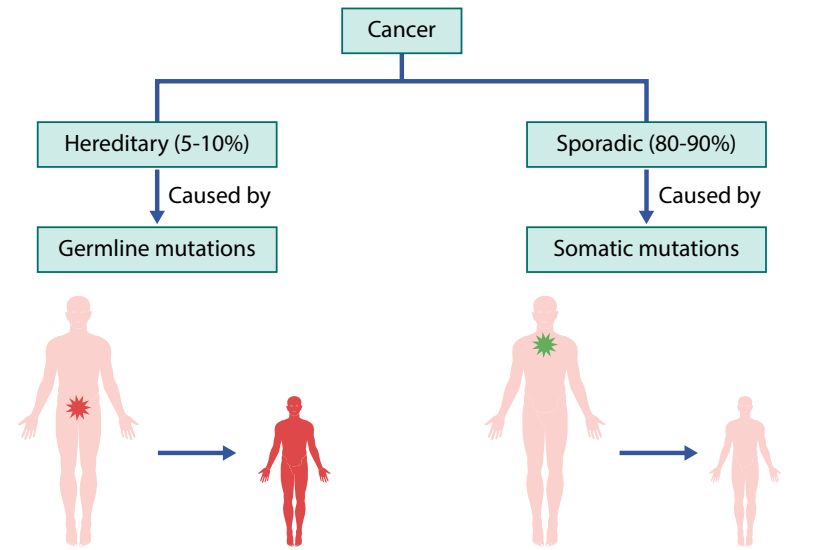


Figure 6.1 The hallmarks of cancer. The illustration shows the six originally proposed hallmarks in addition to the two emerging ones – avoiding immune destruction and deregulating cellular metabolism – and also the two enabling characteristics – tumour-promoting inflammation and genome instability and mutation. Also indicated are drugs targeting some of the hallmarks that are currently in use for the treatment of head and neck cancer (red). Adapted from Hanahan and Weinberg.[79, 80]



- Occur in germline cells: oocytes and spermatozoa
- Are heritable
- Cause cancer family syndromes (e.g. Fanconi anaemia or Li Fraumeni syndrome)

- Occur in non-germline tissues (e.g. head and neck)
- Are not heritable

Figure 6.2 Somatic versus germline mutations. Germline mutations occur in germline cells: oocytes and spermatozoa. They are heritable, and offspring of a person with a somatic mutation will have the same mutation in all cells of their body (e.g. *BRCA1/2* or *RB*, tumour suppressor genes, indicated in red). This increases their chance of developing cancer because only one additional mutation is required to completely inactivate the gene in question (Knudsen's two-hit hypothesis), since most tumour suppressor gene mutations are recessive at a cellular level. Sporadic mutations can occur in any cell in the body (e.g. head and neck cells, indicated in green), spontaneously or as a result of carcinogen exposure. These mutations are not passed onto the offspring unless, by chance, such a mutation occurs in a germline cell. Most cancers are sporadic and are caused by accumulation of somatic mutations. The figures for sporadic and hereditary incidence are for cancers in general. The contribution to head and neck cancer incidence from inherited cancer syndromes is negligible.

implicated in the different complementation groups of this disease have been found to be mutated in sporadic head and neck cancers.[18] (Complementation groups is a genetic term for a situation in which mutations in different genes can cause the same phenotype – in this case, a disease. The term derives from the genetic test for this; if matings between two affected individuals produce healthy offspring, then the mutations cannot be in the same gene. Of course, this only works for a recessive trait.) Other inherited cancer syndromes, including Lynch-II syndrome (genes most commonly implicated include *MSH2*, *6* or *MLH1*), Bloom syndrome (inherited mutations in the *BLM* gene), xeroderma pigmentosum (associated with defects in DNA repair genes: *XPC*, *ERCC2* and *POLH*), ataxia telangiectasia (associated with mutations in the *ATM* gene), and Li-Fraumeni syndrome (mutations in the *TP53* and *CHEK2* genes), have also been found to display an increased risk of head and neck cancers.[19–24] However, only the *TP53* and *CHEK2* genes (and the latter only very rarely) have been found to be mutated in sporadic head and neck cancers, and thus none of these syndromes appear to be major contributors to patient numbers or to a better understanding of the disease head and neck cancer.[18] In 1953, Slaughter et al introduced the concept of 'field cancerization' in oral cancers.[25] This notion can now be understood for head and neck cancers at a molecular level, since we know that these cancers are essentially diseases of sporadic mutations arising through a process of sequential mutations and clonal selection. As mutations arise and the populations of cells harbouring the mutations expand with some ultimately becoming cancers (see **Figure 6.3**), populations of cells that arise early on, do not disappear, but may continue to survive and proliferate, ultimately occupying areas outside that of the cancer.[26] These cells can spread and create the 'fields' of abnormal cells harbouring some critical mutations that may provide the raw material for subsequent primary tumours if not removed or killed by treatment. To understand cancer properly at a molecular level, it is necessary to understand the biological process of evolution through natural selection, since the same forces of mutation and selection acting on individual cells harbouring genetic alterations drive the evolution of a tumour during cancer development. **Figure 6.3** illustrates the process of evolution of malignant cells from normal cells through the acquisition of critical genetic alterations that occurs in cases of sporadic carcinogenesis. As cells acquire mutations, the key issue from a cancer perspective is whether any of the mutations that arise by chance in an individual cell provide a selective survival, or clonal advantage (often referred to somewhat imprecisely as a growth advantage or more correctly as a proliferative advantage). What this means is that cells that acquire characteristics that enable that cell, and all of the daughter cells derived from it, to compete more successfully with the surrounding cells and thus have a selective advantage leading to these cells gradually increasing in number. Eventually such cells can proliferate sufficiently to form a pathologically detectable tumour. Since the causes of the mutations in different types of cancer can vary, we will first look at the processes promoting carcinogenesis in head and neck cancers (when we refer to head and neck cancers we mean squamous cell carcinomas of the head and neck). Then

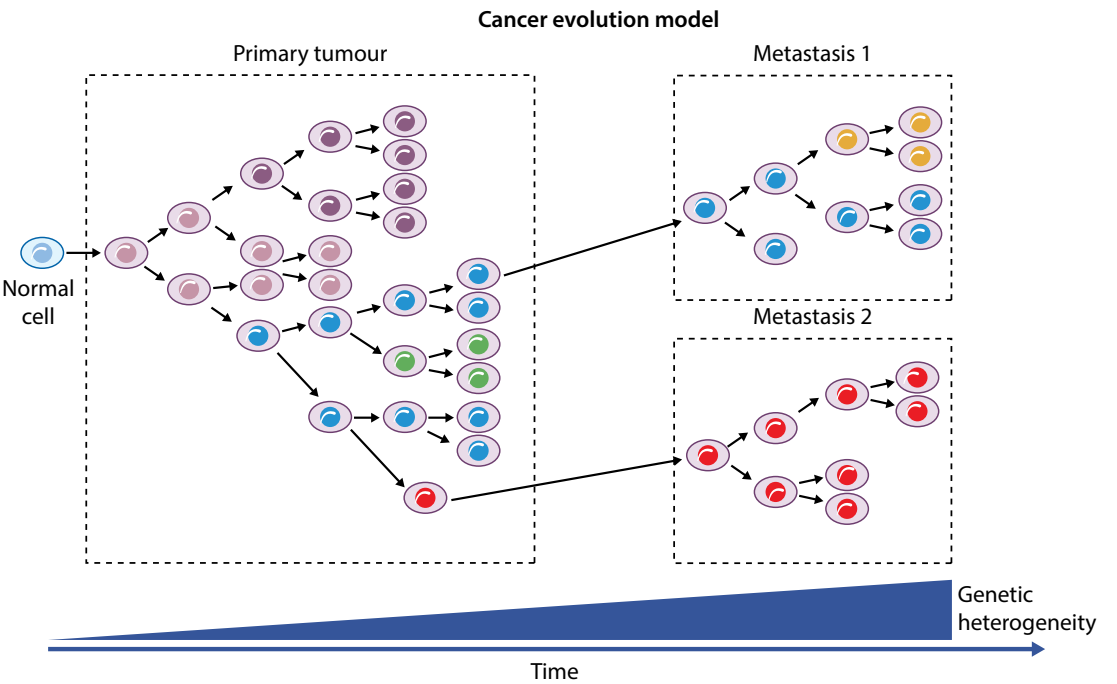


Figure 6.3 Model of cancer evolution. A normal cell (cell with a pale blue nucleus) acquires the initiating somatic mutation giving rise to the founder clone (lavender nucleus). Accumulation of additional mutations will lead to cancer heterogeneity represented by subclones of cells with purple, blue, green and red nuclei. Some of these subclones will acquire metastatic potential (blue and red nuclei) and form metastatic sites (Metastasis 1 and Metastasis 2). Additional mutations can be acquired at any time including post-metastasis (gold nucleus in Metastasis 1). Adapted from Caldas.[27]

we will look at the specific genes that are most frequently altered in head and neck cancers and briefly how these alterations contribute to the disease process.

Mutagenic events, viruses and epigenetic modifications

DNA damage occurs every day in our cells and depending upon the type of damage the frequency can vary from as few as ~10 double stand breaks per cell/day up to ~10^4 bases altered by oxidative damage per cell/day and similar levels of replication errors and single strand breaks.[28] Importantly, much of this DNA damage is repaired and therefore does not lead to stable alterations or mutations. However, DNA damage leads also to mutations being established each day when the damage is not successfully repaired. The most common sources of this DNA damage include normal biochemical processes such as the production of reactive oxygen species (ROS) generated by oxidative phosphorylation through the electron transport chain.[29, 30] Of particular interest for cancers are agents that increase the rates of DNA damage and resulting mutations and thus increase the likelihood of carcinogenesis. In head and neck cancers there are three broadly distinct processes promoting the genetic changes that lead to cancer:

1. Mutations arising from exposure to chemical carcinogens (especially from tobacco smoke and alcohol)
2. Infection by oncogenic viruses (specifically oncogenic strains of HPV), typically leading to loss of tumour suppressor gene (TSG) function
3. Epigenetic modifications, typically leading to loss of TSG expression.

At the present time, the vast majority of data derive from studies from North America and thus the impact of betel quid and asbestos exposure are not being captured by large scale sequencing initiatives, and therefore the undoubted impact of these in some geographical areas remains to be determined by genomic studies.[31, 32]

MUTAGENIC EVENTS

Probably the most significant mutagenic events are those caused by environmental carcinogens, because they affect the most patients and result in cancers with poorer outcomes. The two primary sources of these carcinogens for head and neck cancers are tobacco smoke and alcohol. A critical feature of carcinogenic chemicals is that they often produce chemical modifications, typically of the nucleic acid bases, for which no specific repair pathway exists. This is hardly surprising since the variety of different chemical adducts that smoking alone can cause may exceed one hundred (tobacco smoke contains approximately 50–60 carcinogenic compounds that may display multiple effects on the DNA).[33–35] In contrast, the oxidation of one of the DNA bases, guanine, to 8-oxo-guanine by the endogenous production of ROS – one of the most common chemical modifications of DNA to occur – can be repaired by base excision repair (BER) mechanisms initiated by an enzyme that specifically recognizes this common lesion: 8-oxoguanine glycosylase (OGG1).[36–38]

Alcohol consumption is another major source of risk for developing head and neck cancer.[39–42] Although alcohol may not be chemically as complex a carcinogen as tobacco smoke, the interactions of alcohol with the body are highly complex, ranging from the provocation of an inflammatory response, to mutagenic and epigenetic effects. Alcohol is readily metabolized to acetaldehyde, which is a genotoxin.[43] While most alcohol will be metabolized in the liver, there is good evidence that alcohol is also metabolized in the oral cavity and in the oesophagus.[44, 45] In the oral cavity, the concentrations of acetaldehyde resulting from local alcohol metabolism are estimated to be equivalent to concentrations that have been shown to be mutagenic *in vitro* and, potentially worryingly, this can be achieved by drinks ranging from a single sip of a strong liquor to gargling with an alcohol-containing mouthwash.[46, 47] As with tobacco smoke, the details of alcohol promoted carcinogenesis in the head and neck are too complex to discuss in detail in this chapter. However, to give some idea of the complexities, there is also evidence of carcinogenicity that is not due to the classical ethanol metabolism described above, but rather to additional carcinogenic effects of acetaldehyde that already exists in alcoholic drinks.[48] Further complicating our understanding of this process and the link between alcohol and head and neck cancers is the fact that laryngeal cancer is linked with alcohol as a risk factor,[49–51] but the larynx seems an unlikely site to be directly affected as in normal swallowing action, the alcohol will not come into direct contact with internal laryngeal structures.

Of considerable importance is the interaction between tobacco smoking and alcohol, with several reports suggesting that the interaction leads to a greater than additive effect.[52, 53] It remains unclear how these processes might act synergistically, although it has been suggested that concomitant exposure may alter rates of uptake of some carcinogens and *in vitro* studies support the existence of synergy.[54, 55]

VIRUSES

In the past decade, it has become apparent that a specific subtype of head and neck cancer, with a different biology/molecular biology and significantly different clinical behaviour,[56] has been on the increase. The incidence of OPSCC has risen sharply and this has been particularly apparent in more developed countries.[57–62] This increase has been a surprise, since the smoking incidence has followed a downward trend in most of the developed world,[63] and thus the increase has been observed in the context of a generally stable or even reducing incidence of most head and neck cancers.[64] The most obvious characteristic that distinguishes the vast majority of these patients with OPSCC is the presence of viral DNA derived from the human papilloma virus strain 16 (HPV-16).[57, 65] HPV has long been known as the causative agent of cervical cancers, and so a robust understanding of the oncogenic role of

the virus has been developed.[66] HPV is a double stranded DNA virus (dsDNA); that is, it has a genome that exists as double stranded DNA, and many such viruses (examples include adenoviruses and polyomaviruses) have a strategy to ensure that the infected cell provides the DNA replication machinery needed for viral replication by promoting progression of the cell cycle into S-phase[67] in HPV infection (this involves viral oncoproteins E6 and E7, which are discussed in more detail below). Detailed sequence analysis[18, 68, 69] has shown that HPV+ tumours have fewer mutated genes than similar site of origin HPV– tumours and critically that there are different mutational profiles in HPV+ and HPV– cancers, which may well have important consequences for tumour responses to treatment.[18]

EPIGENETIC MODIFICATIONS

Epigenetic modification of gene expression and function is another major mechanism that promotes cancer in the head and neck. There are many different types of epigenetic changes but the most commonly observed ones with strong links to cancer are the methylation of cytosine residues at so-called CpG islands in the promoter regions of TSGs.[70, 71] (The most common epigenetic modification of DNA is the methylation of cytosine residues to 5-methylcytosine. This occurs predominantly in residues that are 5' to a guanine base, i.e. a CpG site. In many genes the concentration of CpGs is higher in the non-coding promoter regions 'the islands'. Typically, increased methylation of cytosines in CpG islands results in reduced gene transcription; epigenetic silencing.) For example, in head and neck cancers, *CDKN2A (*$p16^{INK4A}$) hypermethylation has been observed to be associated with reduced overall survival in population-based studies.[72–74] Although the enzymes that carry out the methylation of cytosine bases are well known,[75] it is unclear what determines whether a gene will become hyper- or hypo-methylated during the lifetime of an individual. Dietary folate may be one factor, since it ultimately provides the single carbon (i.e. methyl groups) units, but the links between folate levels in diet and gene methylation are complex and often counter-intuitive.[76–78] Some of the genes that are altered in cancers (see below) impact on epigenetic processes, but for the time being, it seems that whilst epigenetic modifications arise, we are not able to say what causes this.

Molecular pathways involved in head and neck cancer

In a recent study from The Cancer Genome Atlas (TCGA), critical and comparatively common mutations were described in 30 genes with mutation frequencies ranging from as high as 80% to as low as 0% for the same gene (this may look like an error, but the gene might be commonly mutated in HPV+ and not mutated in HPV– disease or vice versa), depending on HPV status of the cancer.[18] (HPV+ = HPV positive, i.e. HPV promoted disease, not simply harbouring some HPV DNA; HPV– = HPV negative disease, i.e. disease not driven by HPV, may contain HPV DNA. Whether the disease is driven by HPV or not depends essentially upon whether or not the viral oncogenes E6 and E7 are expressed. Expression of cellular protein $p16^{INK4a}$ is one surrogate biomarker that is linked with HPV+ disease, but it is not 100% specific. See Chapter 13, Oropharyngeal tumours.) In addition, these analyses demonstrated that the majority of tumours harboured copy number alterations (CNAs) with loss of chromosomal regions in 3p and 8p, and gains of 3q, 5p and 8q being the most common.[18] We now know all of the mutations in the whole genome (or in some cases all of the mutations in exon sequences) from several hundred patients with head and neck cancers from a number of studies,[18, 68, 69] and although there is incomplete concordance between studies with respect to the lists of genes identified and the frequency of gene mutations, there is a strong and largely consistent indication of the most frequent and most critical genetic lesions in head and neck cancers. (Exons are the coding parts of gene sequences, in contrast to the introns, which are non-coding and are removed by splicing of the nascent mRNA.) To understand this complex situation, we can simplify the process of carcinogenesis by considering how mutated or silenced genes affect the 'hallmarks of cancer'.

In 2000, Douglas Hanahan and Robert Weinberg published a seminal paper that has been cited more than 14 000 times, introducing their cancer hallmarks.[79] They described how many of the most common mutations that arise in cancers affect six primary, tumour phenotypes or characteristics:

1. Self-sufficiency in growth signals
2. Insensitivity to anti-growth signals
3. Evading apoptosis
4. Limitless replicative potential
5. Sustained angiogenesis
6. Tissue invasion and metastasis.

The significance of this article is that it has provided a clear framework for trying to understand the often complex molecular interactions that have been detected in cancers. The list was augmented in 2011 by the same authors to include enabling characteristics of cancers and two additional emerging hallmarks:[80]

- Enabling characteristics:
  - genome instability and mutation
  - tumour-promoting inflammation
- Emerging hallmarks:
  - Avoiding immune destruction
  - Deregulating cellular energetics.

As we will see, these characteristics are ubiquitous in cancers and understanding the biology that regulates these processes provides a means to incorporate the complex genetic data being generated by the latest technologies.

In 2011, the year that the hallmarks were revisited, an excellent review of head and neck cancer molecular biology was published, based upon a pre-'omic' view of the disease.[26] Considering the 'hallmarks', we can try

to categorize the most frequently mutated genes according to their known roles in these phenotypes. (Note that human gene symbols are typically capitalized and italicized, whereas the protein is not italicized e.g. *TP53* and *MYC* genes encode p53 and MYC proteins. Other species gene symbols usually only capitalize first letters, for example the *Myc* gene in mice or other mammals.) Genes such as *TP53* (p53), *CDKN2A* (p16INK4a), *CCND1* (Cyclin D1), *PIK3CA*, and *MYC*, which were known to be mutated in head and neck cancers, could be identified as having roles in cell cycle regulation (insensitivity to anti-growth signals), cell proliferation (self-sufficiency in growth signals) and cell survival (evading apoptosis). Note though that many commonly mutated 'cancer genes' have roles that impact on more than one hallmark process. So for example, *MYC* is implicated in self-sufficiency in growth signals, insensitivity to anti-growth signals, evading apoptosis and also in acquiring limitless replicative potential, whilst *TP53* has functions that regulate the insensitivity to anti-growth signals, evading apoptosis, acquiring limitless replicative potential, sustained angiogenesis and loss of function has also been linked to tissue invasion and metastasis.[81] If that isn't sufficient, both *MYC* and *TP53* have also been implicated in the deregulation of cellular energetics (see section). In addition, *TP53* has been famously dubbed the 'guardian of the genome' because of its critical role in suppressing one of the 'enabling characteristics': genome instability and mutations.[82] In contrast some 'cancer genes' only appear to impact on one hallmark phenotype. *CDKN2A* is a critical gene for normal cell cycle regulation since it encodes a protein $p16^{INK4a}$ (often simplified to p16),[73, 83] which is a regulator of cyclin dependent kinases that control cell cycle progression (see **Figure 6.4**). Thus mutations or epigenetic suppression of this gene contribute to loss of normal cell cycle control. On its own, this is insufficient to lead to self-sufficiency in growth signals since normal control is retained by the G1-S checkpoint through the *RB* gene, but is sufficient to produce an insensitivity to anti-growth signals that would stimulate p16-mediated G1-S arrest in cells already stimulated to progress through the cell cycle.[85, 86]

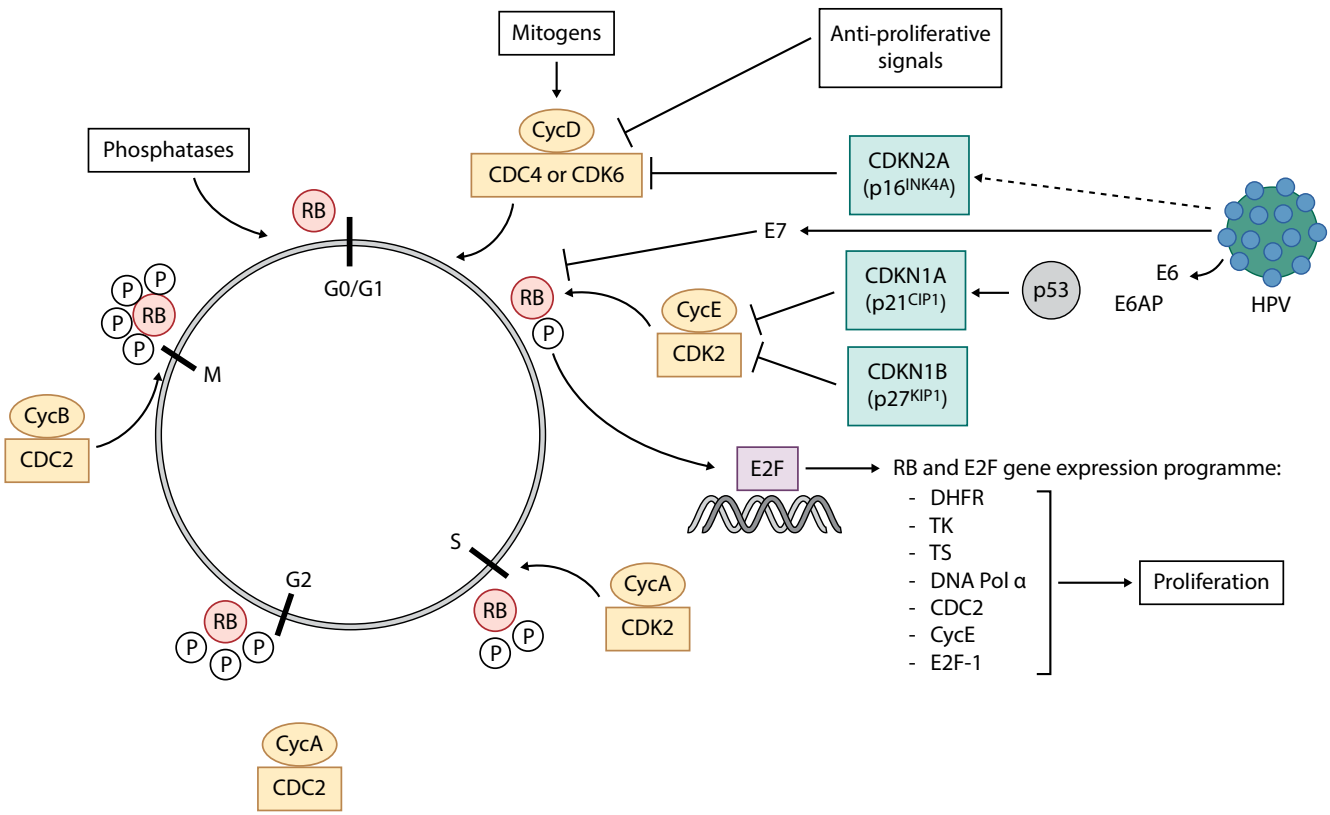


Figure 6.4 Cell cycle regulation. The cell cycle is regulated by coordinated action of cyclins (CycX) and cyclin-dependent kinases (CDKs and CDCs [cell division cycle proteins]) that phosphorylate the RB protein. In the absence of mitogenic signals RB protein is in an under-phosphorylated state and bound to E2F transcription factor rendering E2F inactive. Mitogens activate CycD/CDK4 or CycD/CDK6 complexes that phosphorylate RB protein causing it to release the E2F transcription factor that activates expression of a set of genes that mediate cell cycle progression into S phase, including DNA polymerases and CycE. During the cell cycle RB protein is sequentially phosphorylated by CycE/CDK2, CycA/CDK2, CycA/CDC2 and CycB/CDC2 complexes. Following mitosis RB is de-phosphorylated by phosphatases. Anti-proliferative signals activate $p16^{INK4A}$ protein, encoded by the *CDKN2A* gene that inhibits CycD/CDK4/6 complexes. In response to DNA damage and replication errors p53 protein is activated and up-regulates the transcription of *CDKN1A* gene encoding for CycE/CDK2 inhibitor $p21^{CIP1}$. E6 and E7 proteins, encoded by the HPV genome, target p53 and RB respectively, causing an increase in cellular proliferation. Molecules implicated in head and neck cancer are marked in red. Adapted from Knudsen ES, Knudsen KE.[84]

If the above seems complicated, then the current situation in the now 'omic' era is potentially more daunting because, in the last few years, the amount of genetic data that is available on cancer has been significantly expanded by genomic (and other 'omic') analyses of many different types of cancer. However, whilst the quantity of data has expanded phenomenally, the essential understanding of the disease has not changed too much and in many ways has actually become clearer. Whole genome sequencing (WGS) and whole exome sequencing (WES) of cancer genomes have become fairly routine thanks to the development of so called next-generation or high-throughput/second-generation sequencing technology. As a result, several studies have examined the head and neck cancer genome using a range of different technology platforms,[68, 69] with the most extensive recent studies, already alluded to above, coming from the TCGA consortium.[18]

These studies have confirmed the findings of many older studies that had, for example, correctly identified that the most commonly mutated gene in head and neck cancers was the *TP53* tumour suppressor. In addition, however, these studies identified several genes as harbouring mutations in head and neck cancers that had not been identified by earlier studies.

Another feature of head and neck cancers that has been illuminated by WGS and WES analysis of tumours has been the detection of distinct mutational profiles associated with specific carcinogens or with viral oncogenesis.[18] For example, where smoking and/or drinking contribute to tumorigenesis, then distinctive mutational spectra are observed that are linked with the carcinogen and its mode of action.[87–89] This includes C>A substitutions (identical but complementary to G>T referred to in some of the older of these papers), which are greatly increased in larynx cancers in smokers and it is known that these mutations can be induced by polycyclic aromatic hydrocarbons such as benzo[a]pyrene (for more detail on smoking and mutations induced in cancers, see the excellent recent study by Alexandrov et al[89]). Interestingly, this signature is much less obvious in oral cavity cancers, even though pack years correlate with mutational frequency in oral cancers.[90, 91]

As explained above, epigenetic regulation is an important mechanism contributing to carcinogenesis to the extent that it has been proposed by some as an additional emerging hallmark in cancer development[92–94] (Jones and Baylin, 2002; Muntean and Hess, 2009; Dawson and Kouzarides, 2012). Considerable evidence points to epigenetic alterations playing an important role in the development of head and neck cancers,[70, 95] and data from genomic studies also support this conclusion. For example, the TCGA network found mutations in the histone H3 methyltransferase gene MLL2 in 18% of head and neck cancers studied.[18]

In addition to mutations in genes that catalyse the creation (e.g. methyltransferases) or removal (e.g. demethylases) of epigenetic modifications, other events contribute to this process since gene methylation has been observed to change with time in 'normal' ageing tissues[96] and ageing and cancer are biologically linked processes.[96–99] Whilst it is not known what environmental (such as dietary) factors determine or affect changes in epigenetic regulation, it is clear that some specific genes are modified epigenetically more than others and that this alters the level of expression, typically leading to silencing (down-regulation) of TSGs in head and neck cancers.[70] This occurs in both HPV+ and HPV– carcinogenesis, but the genes that are altered may differ depending on the presence or absence of HPV (see below and also Chapter 13, Oropharyngeal tumours).[18]

The impact of specific genes on the hallmarks of head and neck cancer

Examining the pathways that are affected by mutations in head and neck cancers it is immediately apparent that there are two clearly different patterns of genetic alterations, and which genes are mutated depends to a significant extent upon whether the disease has been promoted by HPV or not.[18, 68, 69] A note of caution needs to be added here: categorization is a human approach to simplifying complex systems; we like to pigeonhole things. But in reality, genes and gene function don't really fit into the neat characteristics to which we want to reduce cancer cell pathways.

LOSS OF CELL CYCLE CONTROL (INSENSITIVITY TO ANTI-GROWTH SIGNALS)

The most common pathway affected in both HPV+ and HPV– disease is loss of normal cell cycle control, which occurs in 90–100% of both types of cancer (genes most commonly implicated: *TP53, RB1, CDKN2A, CCND1, E2F1, MYC, HPV E6*, and *HPV E7*). This pathway primarily regulates the hallmark insensitivity to anti-growth signals, but also impacts upon evading apoptosis and limitless replicative potential and sustained angiogenesis.

TP53

The most common mutations in cancer generally, and in head and neck cancer specifically, affect the *TP53* gene, which has been found to be mutated in approximately 50–60% of all head and neck cancers.[100–109] TCGA network analysis showed that this varied from approximately 80% in HPV– cancers, to 0% in HPV+ cancers.[18] This difference is not surprising, since HPV is oncogenic in part because it can inactivate the p53 protein encoded by the *TP53* gene (discussed below).[18, 110, 111] Importantly, loss of p53 function, typically as a consequence of missense mutations, has been found to be associated with patient outcomes in head and neck cancers with patients harbouring disruptive mutations that compromise p53 function displaying reduced overall survival compared to those with wild-type or non-disruptive mutations.[112, 113] Missense point mutations change the codon such that a different amino acid is encoded (cf. nonsense mutations that introduce a premature stop codon into the sequence). Generally tumour suppressors are inactivated by either nonsense or

missense point mutations, whereas oncogenes can only usually be activated by a very limited number of missense point mutations (not surprisingly, since most amino acid substitutions are more likely by chance to have a negative effect on protein function. Disruptive mutations = non-conservative amino acid substitutions in critical parts of the DNA binding domain. Wild-type = normal, the form of the gene found in the wild, non-disruptive mutations of TP53 = amino acid substitutions that do not disrupt DNA binding or only have a limited effect upon transcription regulations by p53).

The p53 protein functions primarily as a sequence specific DNA binding protein[114] that regulates the expression of a considerable number of genes (estimates range from a few hundred to more than a thousand). p53 protein is a potent inducer of apoptosis (programmed cell death) and so it is not surprising to find that under normal circumstances not one but two genes (*MDM2* and *MDM4*) are responsible for maintaining p53 at low levels in an inactive form. However, following a wide range of cellular stresses, in particular genotoxic stresses (stress induced by damaging DNA), p53 and MDM2 interaction is prevented resulting in an increase in the p53 protein level and a consequent up-regulation of p53 target genes that may mediate cell cycle arrest or apoptosis depending upon the nature of the damage. For more detailed descriptions of the role of p53 and the consequences of loss of p53 function in cancer in general and in head and neck cancer respectively, we direct the reader to Vousden and Lane[114] and Loyo et al respectively.[115]

RB, E2F1 and CDKN2A

RB was the first TSG to be identified and any treatise on the *RB* gene will usually include mention of Alfred Knudsen, retinoblastoma, and the two-hit hypothesis that he proposed.[84, 116, 117] *RB* functions to regulate the G1-S phase transition of the cell cycle and it does this by binding to and inhibiting the activity of a family of transcription factors called E2Fs. As the cell enters the cell cycle at the G1 phase in response to mitogenic signalling (see **Figure 6.4**), the signal passes intracellularly from the activated transmembrane receptor molecules at the cell surface to promote the transcription of cyclins. (Mitogenic signals are induced by mitogens: factors that stimulate mitosis such as growth factors e.g. epidermal growth factor (EGF).) Cyclins that are produced then bind to cyclin-dependent kinases (CDKs) that perform phosphorylation reactions targeting a range of genes, one of these being *RB*.[84] Phosphorylation of RB leads to inactivation of RB since it no longer binds to E2F and as a result, E2Fs promote transcription of their target genes, which *inter alia* includes genes involved in DNA synthesis i.e. S-phase (see **Figure 6.4**). As a consequence, RB not only regulates the cell cycle, but also regulates the cell cycle arrest that is a requirement for terminal differentiation (which is frequently regulated by RB related proteins p107 and p130).[118, 119]

Frequently inactivated in head and neck cancers by promoter hypermethylation, the *CDKN2A* gene encodes two proteins with tumour suppressor activities (p14 [$p14_{ARF}$] and p16 [$p16_{INK4a}$]). p16 inactivation, either through mutation or via promoter hypermethylation has been implicated in many cancers.[120, 121] p16 functions as a negative regulator implicated in many cancers.[120, 121] p16 functions as a negative regulator of G1-S phase progression that acts by binding to and inhibiting the cyclin dependent kinases CDK4 and CDK6.[122] (Some TSGs, including *CDKN2A*, become transcriptionally repressed as a consequence of increased promoter methylation. This can arise as an individual ages, or may be associated with disease. In cancer, changes in methylation of CpG islands (both increases and reductions in methylation) are commonly observed, and loss of *CDKN2A* function either through mutation or increased promoter methylation is a common event affecting more than 50% of HPV– head and neck cancers.)

CCND1 and let-7c

Cyclin D1 is the protein encoded by the *CCND1* gene and this gene has frequently been found to be amplified in a range of cancers including head and neck cancers.[18, 123–125] Cyclins are the critical regulators of the cell cycle and are typically short-lived proteins that are regulated transcriptionally.[126, 127] In the case of cyclin D1, expression is regulated by the MAPK pathway, which is activated following receptor mediated tyrosine kinase activation, by for example, growth factors (EGF binds to the EGF receptor EGFR, see **Figure 6.4**), cyclin D1 associates with cyclin dependent kinases 4 and 6 to promote phosphorylation of target proteins, in particular of the RB TSG leading to its inactivation and cell cycle progression. Thus, gene amplification of *CCND1* provides for constitutively increased cyclin D expression and loss of normal cell cycle regulation at the G1-S checkpoint.[128] let-7c is a microRNA (miRNA) that regulates a number of target genes and that has been found to be down-regulated/deleted in approximately 40% of HPV– head and neck cancers and this was associated with increased *CDK6* expression, anticipated to promote cell cycle progression in combination with *CCND1*.

MYC

The role of the *MYC* gene (also called *c-MYC* or *cMYC* to distinguish it from the viral oncogene originally identified as the v-Myc gene from the avian myelocytomatosis virus and from two other alleles in the human genome: *N-MYC* and *L-MYC*)[129] in cancer has a long and fascinating history due ultimately to the complexity of MYC functions with roles in cell cycle regulation, cell proliferation, cell survival/apoptosis, and more recently identified roles in cancer cell metabolism.[130–135] One of the reasons that *MYC* function has proven difficult to dissect is that MYC has effects on a huge number of genes including *CCND1*, *TP53* and *TERT* (Telomerase – a gene implicated in immortalization of cancer cells).[131, 136] MYC functions as a hetero-dimer to regulate transcription associating with either MAX, leading to activation of gene expression, or with MAD leading to repression of gene expression to regulate control of critical genes that are required for cell

proliferation and survival. More recently it has been found that *MYC* acts not only to regulate the initiation of gene expression similar to many other transcriptional regulators, but also affects other aspects of transcription and post-transcriptional processes such as modulating the stability of newly synthesized RNA molecules and through these additional activities MYC has been revealed to exert an ever greater impact on gene expression.[137] Amplification of the *MYC* locus occurs in over 10% of HPV– cancers, leading to increased MYC signalling and thus promoting cell survival and proliferation.

HPV E6, E7 and E2F1

Human papilloma viruses are doubled stranded DNA viruses that require the host cell DNA replication machinery for viral genome replication.[138] WGS and WES analyses reveal clear differences in the patterns of genetic alterations between HPV+ and HPV– head and neck cancers (note that the vast majority of HPV+ head and neck cancers are derived from the oropharynx).[18, 68, 69, 74, 115] HPV encodes two critical onco-proteins: E6 and E7 that promote S-phase progression in infected cells (see **Figure 6.4**). Together these viral oncogenes inactivate two TSGs, *TP53* and *RB* respectively,[139] with the consequence of promoting S-phase progression in cells.[138]

Normally, this leads to viral DNA replication, and virion assembly and production, which may also lead to cell death. Rarely however, the infection can become abortive, either as a result of recombination leading to integration of part of the viral genome into the host cell genome or as result of the effects of E6 and E7 expressed as episomal genes in a cell that therefore fails to continue to differentiate preventing late gene expression.[140] (Episomal DNA is DNA that can be replicated independently of the chromosomal DNA, typically unintegrated into the genome.) Providing that the infected cell retains both of the oncogenic genes (E6 and E7), this can promote deregulated cell cycle progression through the G1-S checkpoint in the cell, and in all of the daughter cells it produces. The accumulation of a population of cells harbouring such a defect significantly increases the risk of carcinogenesis since two critical TSGs are already inactivated in all of these cells. Another consequence of HPV-mediated TSG inactivation is that fewer additional events are required for tumorigenesis.[68, 69]

E6 functions by binding to the p53 protein and it also binds to a cellular protein E6AP (encoded by the *UBE3A* gene [ubiquitin-protein ligase E3A]), which promotes the poly-ubiquitylation of p53 and thus targets p53 protein to the 26S proteasome for degradation.[141, 142] E7 functions by binding to the RB protein and preventing it from interacting with E2Fs, thus allowing E2F-regulated genes to become transcribed.[143] Recent studies have also identified that binding of E7 to RB also promotes degradation of the RB protein by the ubiquitin – proteasome route.[144, 145] In HPV+ cancers, E6 and E7 expression appear to be ubiquitous, further supporting a role for retaining expression of these to maintain continued cell cycling. In HPV+ cancers, *E2F1* expression was also often increased (in approximately 19% of tumours); this would be expected to result from inactivation of the *RB* and *TP53* genes by E7 and E6 respectively.

Curiously, although we know so much about RB, and we know that loss of RB function resulting from inactivation by HPV E7 protein (see below) leads to upregulation of p16 (*CDKN2A* expression), we do not at the present time know exactly why this is so. Clearly RB represses expression of p16, but since p16 is not known to be a direct target of any of the E2F family of transcription factors that RB suppresses the details remain obscure.

GROWTH AND PROLIFERATION SIGNALLING (SELF-SUFFICIENCY IN GROWTH SIGNALS)

The next most frequently altered pathway identified is the receptor tyrosine kinase (RTK) signalling pathway that regulates the mitogen activated protein kinase (MAPK) signalling pathway. This primarily controls the hallmark: self-sufficiency in growth signals. Genes that regulate this pathway are altered in approximately 60% of head and neck cancers regardless of HPV status (most commonly implicated genes: *PIK3CA, EGFR* and *PTEN* plus *CCND1* and *MYC* listed above).

EGFR, PTEN and PIK3CA

In normal cells the signalling pathway that promotes cell entry into the cell cycle is stimulated in epithelial cells by a soluble ligand mitogen the epidermal growth factor EGF.[146] EGF binds to the extracellular domain of the epidermal growth factor receptor EGFR, a transmembrane receptor protein that has intracellular tyrosine kinase activity (the ability to catalyse the transfer of phosphate onto specific tyrosine residues in substrate proteins). Binding of the EGF receptor ligand causes the receptor to dimerize at the cell surface, which promotes activation of the RTK activity leading it to phosphorylate substrates on tyrosine residues (see **Figure 6.5**). Target proteins that are post-translationally modified by phosphorylation include the receptor itself (auto-phosphorylation) and proteins of the MAPK pathway.[147]

PIK3CA encodes the enzyme phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit (also called p110α), which is the catalytic subunit of a heterodimeric enzyme that catalyses the addition of phosphate from ATP to phosphoinositol lipids that regulate a number of signalling pathways, specifically converting PIP2 to PIP3 and thus activating AKT (also known as protein kinase B or PKB) which plays an important role in cell survival and also regulates several other pathways including ones that control cell movement and metabolism. (PIP2 is phosphatidylinositol (4,5)-bisphosphate; PIP 3 is phosphatidylinositol (3,4,5)-trisphosphate (PtdIns(3,4,5)P3).) This conversion of PIP2 to PIP3 is part of the signalling pathway from RTKs that ultimately controls a wide range of cellular signalling programmes including transcriptional programs that activate progression through the cell cycle and non-transcriptional survival programs such as activating the mTOR pathway that promotes protein synthesis

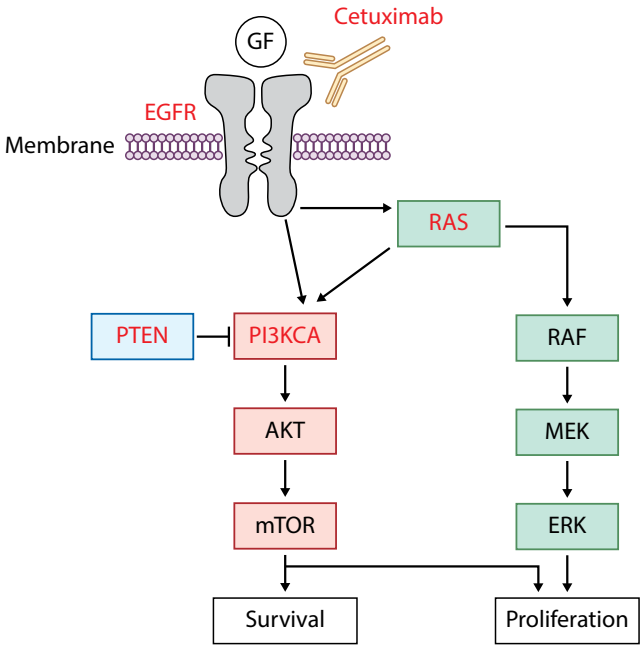


Figure 6.5 Epidermal growth factor receptor (EGFR) pathway. Upon binding of the mitogenic ligand/growth factor (GF) such as EGF (epidermal growth factor), EGFR undergoes dimerization and auto-phosphorylation initiating intracellular signalling via several pathways including the RAS-mediated protein kinase pathway and PI3K/AKT survival pathway. Activation of RAS leads to a signalling cascade involving several mitogen-activated protein kinases (MAPK), including MEK and ERK ultimately leading to cellular proliferation. Activation of the PI3K/AKT pathway is involved in cellular proliferation as well as in apoptosis resistance (survival) via activation of mTOR. PI3KCA is a catalytic subunit of PI3K often mutated in head and neck cancer. Tumour suppressor PTEN is an inhibitor of PI3K/AKT pathway that often undergoes inactivating mutations in head and neck cancer. Cetuximab is a monoclonal antibody that binds to the EGFR that inhibits activation of the EGFR pathway (and recruits antigen directed cell cytotoxicity) and is used clinically for the treatment of metastatic head and neck cancer. Molecules implicated in head and neck cancer are marked in red. Adapted from Ladanyi and Pao.[150]

needed for cell growth as part of the process of promoting cell proliferation and survival.[148, 149] The reverse reaction, converting PIP3 to PIP2, is, interestingly, carried out by the product of the other commonly mutated gene in head and neck cancers, the *PTEN* gene, which encodes an enzyme: the phosphatase and tensin homolog.[151–153]

In head and neck cancers, localized amplifications of the EGFR gene located on chromosome 7 occur in more than 10% of cases and amplification presumably leads to increased signalling from the receptor.[18] Mutations in PIK3CA are common in HPV– cancers (>30% of cases), but are significantly more common in HPV+ cancer (>60% of cases). Typically mutations in PIK3CA were concentrated in three hotspots that are known to lead to constitutive activation of the protein, whereas for PTEN, which functions as TSG to oppose the activity of PIK3CA (and therefore also of EGFR activation), mutations typically inactivate the protein and may be nonsense or missense point mutations. Thus all three of these genes have roles in the same signalling pathway to promote cell growth, proliferation and survival, and mutations in these compromise normal cell signalling and the regulation of cell growth, proliferation and survival.

CELL DIFFERENTIATION REGULATION (LIMITLESS REPLICATIVE POTENTIAL)

The third most commonly affected pathway implicated in between 40% and 60% of HPV+ and HPV– cancers respectively controls cellular differentiation of the squamous epithelium.[18] De-differentiation and the suppression of normal differentiation are prerequisites for immortalization (terminally differentiated cells exit the cell cycle and so do not replicate further) and in the case of HPV+ cancers, arresting differentiation is likely to promote early gene expression at the expense of late gene expression with the predicted consequence of cellular transformation being promoted over viral production.[154] Genes implicated specifically in this pathway include *TP63, NOTCH* and *FAT1*, but also *MYC* which has been shown to upregulate *TERT*,[155] in addition to having a role in cell cycle regulation, cell proliferation and survival.

TP63, NOTCH and FAT1

One of the first new discoveries to come from the early genome wide analyses was that *NOTCH1* (and more rarely other alleles *NOTCH2* and *NOTCH3*) was mutated in a significant percentage of head and neck cancers and moreover that the mutations would be predicted to inactivate NOTCH function.[68, 69] *NOTCH* is best understood because of its role in preventing differentiation of stem cells and through this contributing to their proliferative capacity.[156] Thus mutations that inactivate *NOTCH* would appear to have an anti-proliferative effect and might even promote differentiation. More recently, it has been found that *NOTCH*, and also *FAT1* (also mutated predominantly in HPV– head and neck cancers) negatively regulate the critical *WNT*-gene target β-catenin (encoded by the *CTNNB1* gene) (see **Figure 6.6**).[125, 157] This function might provide an explanation for the presence of *NOTCH* mutations in HPV+ and HPV– cancers (and also for *FAT1*, which is predominantly mutated in HPV– disease). The WNT signalling pathway has been long studied for its role in colorectal cancers (CRCs), and indeed studies of mutations in CRC led to the creation by Bert Vogelstein and his colleagues of what became known as the 'Vogelgram' illustrating the sequence of genetic events and the associated phenotypic changes that commonly occur in CRC as the disease progresses.[158, 159] *TP63* was originally discovered because of sequence homology in its DNA binding domain with that of the p53 tumour suppressor,[160] and subsequent studies have revealed a complex splicing pattern for the gene that can produce p63 isoforms, which display either positive or negative effects on p63 mediated transcription that normally plays a role in squamous epithelial differentiation.[161–163] (Isoforms are two or more forms of a protein that have similar but non-identical sequences (one may be simply shorter), usually

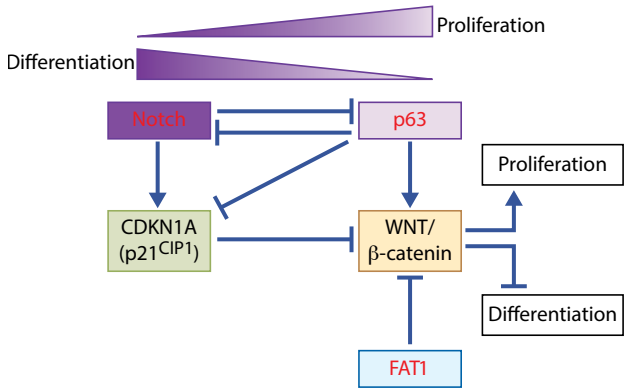


Figure 6.6 NOTCH, p63 and FAT1-mediated regulation of cellular proliferation and differentiation. NOTCH-p63 interplay maintains the balance between cellular proliferation and differentiation. Generally speaking NOTCH promotes cellular differentiation via activation of $p21^{CIP1}$ that suppresses the inhibitory activity of the WNT/β-catenin pathway on the process of differentiation. p63 has the opposite effect by inhibiting $p21^{CIP1}$ as well as by activating WNT/β-catenin pathway that results in an increase in cellular proliferation. In addition, tumour suppressor FAT1 that is frequently inactivated in head and neck cancer inhibits WNT/β-catenin pathway leading to a decrease in cellular proliferation. Molecules implicated in head and neck cancer are marked in red. Adapted from Dotto.[164]

produced by differences in the way that the exons are spliced together or because transcription initiates in different places in the gene.) Thus, changes in splicing would result in altered cellular differentiation and consequently proliferation, with the specific effects depending upon the ratios of expression between splice variants.[165]

CELL DEATH REGULATION (EVADING APOPTOSIS)

The fourth most commonly affected pathway with specific mutations identified in 30–40% of head and neck cancers impacts upon the regulation of cell survival and death, which also impacts upon inflammation and immunity. These disparate responses are partly co-ordinated by the NF-κB pathway.[166–168] Genes implicated in this pathway include *FADD, TRAF3* and *CASP8*, but also the genes *TP53, MYC* and *PIK3CA* already listed above for their roles in cell cycle regulation and survival and cell proliferation signalling. At the present time how these genes contribute to tumorigenesis is not as well understood as the roles of the more extensively studied cell cycle and growth and proliferative pathway genes.

FADD, CASP8 and TRAF3

FADD (fas-associated protein with death domain) has been found to be amplified, predominantly in HPV– cancers, and in several instances, the *FADD* gene was found to be co-amplified with the cyclin D *CCND1* gene, which may suggest an interaction between these.[18] FADD links so-called death receptors such as FAS and TNFR1 (tumour necrosis factor receptor 1), which are transmembrane proteins that connect extracellular signals regulating cell survival and death with the intracellular survival regulatory machinery via NF-κB and also with caspase effectors of apoptosis such as caspase 8 (encoded by *CASP8*).[169] *CASP8* encodes the critical effector caspase 8 for the so-called extrinsic apoptotic signalling pathway and in head and neck cancers. *CASP8* inactivating mutations (found predominantly in oral cavity tumours) were often found associated with wild-type *TP53* (thus p53 is competent to induce apoptosis through the intrinsic pathway but caspase 8 which acts through the extrinsic pathways is not).[170] (There are essentially two main effector pathways for apoptosis: the extrinsic, regulated by cell surface receptor signalling; and the intrinsic, regulated by intracellular stimuli such as DNA damage, hypoxia and metabolic stresses.)[170] *TRAF3* is a member of the TNF receptor associated factor (TRAF) protein family, which mediates signals from transmembrane receptor proteins of the TNF (tumour necrosis factor) such as TNFR1 (which acts via FADD see above). *TRAF3* mutations were almost exclusively found in HPV+ disease, which is interesting since TRAFs have been implicated in anti-viral responses mediated by interferons and several viruses inactivate TRAF proteins.[171, 172]

Inflammation is a known risk factor for promoting carcinogenesis[173, 174] and one of the key regulators of inflammatory responses is the gene *NF-κB*.[175, 176] It seems likely that genes such as *FADD*, *TRAF3* and also *PIK3CA*, *TP53* and *MYC* impact on the regulation of NF-κB activity and thus impact on inflammatory processes.

SUSTAINED ANGIOGENESIS

Tumour hypoxia is a well recognized phenomenon that arises as a consequence of increasing tumour size and poor local vascularization.[177] Hypoxia is linked with radioresistance, and is also an independent predictor of poor prognosis.[178] Tumours typically adapt to combat hypoxia through altering transcriptional programs regulated by the oxygen-sensitive hypoxia inducible factor 1α gene; *HIF1α*.[179, 180] Analyses of head and neck cancer genomes might at first sight appear to reveal only limited genetic evidence of frequent disruption of angiogenic regulatory processes. However, common mutations such as those in *TP53* likely alter angiogenesis; for example, p53 has been reported to regulate expression of angiogenesis suppressor thrombospondin 1 (*THBS1*) and also promotes degradation of HIF1α, and in so doing suppresses neoangiogenesis.[181] In addition, several other genes identified through genomic analyses in head and neck cancers including *FADD*, *TRAF3*, *CASP8*, *PIK3CA* and *MYC* that alter signalling through NF-κB are known to affect angiogenesis[182] (as well as invasion and metastasis, see below), and thus some of the most common mutations that occur in head and neck cancers likely have an impact on angiogenesis.

TISSUE INVASION AND METASTASIS

The ability of cancer cells to invade surrounding tissue and metastasize to distant sites is one of the hallmarks of

cancer (**Figure 6.1**) and is also the leading cause of morbidity and mortality in cancer patients.[80] Metastasis is a complex, multistep process during which cancer cells need to leave the primary tumour site, invade the surrounding tissue, intravasate the lymphatic or vascular circulation, survive in the circulation in order to arrive at the metastatic site where they extravasate and establish a secondary tumour.[183] Epithelial-mesenchymal transition (EMT), a process during which cancer cells acquire mesenchymal phenotype characterized by increased migratory and invasive capabilities, is an integral part of the metastatic phenotype.[184] Several molecular pathways that play a role in metastasis have been identified, including signalling from the TGFβ (transforming growth factor β) pathway that has been shown to be important for EMT in a number of cancers, including head and neck cancer.[185] Indeed, mutations and deletions of *TGFβR2* (transforming growth factor β receptor 2) have been found mostly in oral cavity tumours.[185] In addition, deletions in *SMAD4* (Sma + Mad 4, for 'Mothers against decapentaplegic homolog 4'), a transcription factor that is a member of TGFβ pathway, were identified in particular in HPV–head and neck cancers.[18, 185]

Emerging hallmarks

AVOIDING IMMUNE DESTRUCTION

It has been well documented that the interactions between cancer cells and the surrounding stroma or microenvironment play a role in the initiation and progression of cancer and ultimately determine patient prognosis.[186] Tumour microenvironment consists of a number of components, including extracellular matrix (ECM), blood vessels, immune system cells and fibroblasts. More recently, the immune system and its role in carcinogenesis have come into focus with development of drugs that suppress the ability of cancer cells to avoid destruction by the immune system. In particular, PD-1/PD-L1 interaction inhibitors have shown potential for the treatment of a number of cancers, including lung, metastatic melanoma and kidney cancer.[187, 188] Following positive outcomes in several clinical trials, nivolumab, a PD-1 inhibitor, has been approved by the FDA for the treatment of several cancers including head and neck cancer.[189, 190] In depth analysis of the immune microenvironment has demonstrated that head and neck cancer is characterized by high levels of immune cells infiltration and immunosuppression, regardless of HPV status.[191] In particular, as a result of these studies regulatory T (Treg) and natural killer (NK) cells have emerged as potential therapeutic targets.

DEREGULATING CELLULAR ENERGETICS

As long ago as the 1920s Otto Warburg performed experiments on tumours aimed at determining the metabolic processes used by cells in the tumour, which revealed high levels of glycolysis ('fermentation') as well as respiration typical of normal tissues.[192] However, it was not until the 1950s that more quantitative experiments revealed that tumour cells generate much of their energy from fermentation (i.e. glycolysis) whereas normal cells typically use mostly respiration.[193] This observation has been put to good use in PET-CT using the increased capacity of tumour to uptake a radioactive glucose analogue to image tumours.[194] It seems extraordinary, but it is only in the last decade or so that cancer biology has begun to focus in earnest on the so-called Warburg effect, namely the tendency for cancer cells to obtain substantial amounts of energy from aerobic glycolysis. This effect is so ubiquitous that many are now trying to take advantage of this phenomenon for therapeutic purposes. Many of the genes found altered in head and neck cancers have been implicated in metabolic alterations in cancer cells, chief amongst these being *TP53*,[195] *MYC*[196] and *PIK3CA*,[197] all of which have been shown *in vitro* to modulate cancer metabolic profiles. In the case of *TP53*, studies have already identified potential strategies for therapeutic interventions.[198]

CONCLUDING REMARKS

Ultimately what matters is how the enormous amounts of data now being generated by the research community can be used to impact upon patients, whether it be through developing diagnostics or devising new or more precisely targeted treatments (precision medicine). We now know essentially all of the gene mutations that commonly arise regardless of HPV status, but many of these events present huge challenges for exploitation for therapy. Many of the genes that are activated in cancer cells (oncogenes), have important normal functions in cell growth and proliferation (and survival) and thus selective targeting may prove difficult. Rescuing loss of TSG function is even more challenging. Immunotherapy appears to hold great promise and trials of nivolumab (recently approved by the FDA for treatment of head and neck cancers) and other similar agents are ongoing. Another relatively new area of research that seems likely to lead to novel therapeutic approaches is targeting of tumour metabolism, which is already being used in some other cancers such as renal cancer.[199, 200]

Regardless, what these genomic analyses reveal is that there are identifiable molecular pathways that regulate the key processes, the hallmarks, that are altered in cancers of cell cycle regulation, cell survival and death, cellular differentiation, oxidative stress, immunity and some of these impact also on inflammation, angiogenesis and cell migration (invasion). It seems highly likely that new agents that target aspects of these pathways/molecules will be developed; the problem may be one of availability due to the diminishing returns resulting from the cost of developing so many specialized therapeutic molecules for ever more precisely defined molecular subsets of patients.

KEY POINTS

- Cancer is essentially a genetic disease resulting from an accumulation of somatic mutations (no mutations = no cancer).
- Head and neck squamous cell carcinomas are promoted by carcinogens found in tobacco smoke and alcohol (which act synergistically), or exposure to the HPV (OPSCC), or to other carcinogenic substances such as are found in betel quid.
- Genome wide studies have revealed essentially all of the critical gene mutations that occur in head and neck cancers in North American populations, as well as the changes in gene expression and epigenetic alterations that arise in patients with tobacco smoking/alcohol drinking and HPV-associated tumours (we do not currently have similar detailed data from patients from other high-risk exposure activities e.g. betel chewing).
- The potential exists to obtain genome wide data from individual patient tumours. However at the present time the usefulness of such information is limited.
- Cancer cells display characteristic phenotypes that have been called the 'Hallmarks of Cancer' and we can understand the role of genetic and epigenetic changes in cancer cells in the context of these Hallmarks.
- The most commonly affected cellular genes in head and neck squamous cell carcinomas are: *TP53, PIK3CA, CDKN2A, NOTCH, FADD, let-7c, FAT1, CCND1, PTEN, TP63, EGFR and MYC*.
- In HPV driven disease the viral genes E6 and E7 are critical.

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CHAPTER 7

NASAL CAVITY AND PARANASAL SINUS MALIGNANCY

Cyrus Kerawala, Peter Clarke and Kate Newbold

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SEARCH STRATEGY

Data in this chapter may be updated by a Pubmed search using the generic keywords: 'nasal cavity neoplasms' and 'paranasal sinus neoplasms' but focusing on the diagnosis and management of these conditions.

INTRODUCTION

In this chapter, we discuss the management of malignant tumours that develop in the nasal cavity and paranasal sinuses. Malignant conditions involving the nasal vestibule and external nose are discussed in Chapter 85, Nasal reconstruction.

Sinonasal malignancies are a diverse group of tumours, some of which are unique to the nose. They are uncommon, accounting for less than 1% of all neoplasms. Initially they produce little in the way of symptoms and in the early stages can be misdiagnosed as more common benign conditions such as rhinosinusitis. As a result, the diagnosis is often delayed and only made at a relatively advanced stage when symptoms caused by local disease extension supervene. The average delay between the first symptom and diagnosis is approximately 6 months. By the time of presentation erosion of bone and infiltration of sensory nerves may have produced facial pain and concurrent sensory deficits. Extension of the tumour into the orbit, brain and infratemporal fossa not only produce further symptoms but also have profound implications on treatment and likely outcome in terms of both morbidity and prognosis.

Accurate staging of nasal and sinus tumours remains difficult despite recent advances in endoscopy and almost universal access to refined radiological cross-sectional imaging techniques such as CT and MRI. Current staging systems are only applicable to maxillary and ethmoid sinuses.

Surgery and radiotherapy remain the mainstays of treatment. All treatment regimens inflict considerable morbidity including facial disfigurement, altered mastication and, in some cases, loss of sight. The prognosis for patients with sinonasal malignancies has improved over the last three decades but remains relatively poor compared with other head and neck subsites. Consequently, quality of life issues are of particular importance when considering treatment options, particularly in those presenting with extensive disease.

EPIDEMIOLOGY

Sinonasal malignancies have an incidence of 0.5–1 per 100 000 per year.[1] They account for 0.2–0.8% of all malignancies and 3% of upper aerodigestive tract neoplasms.[2] Most develop in the fifth and sixth decades of life. The incidence in men is twice that of women.[3] The misconception that certain races are more susceptible than others to sinus malignancies is explicable by occupational exposure to carcinogens.[2]

AETIOLOGY

Several carcinogenic compounds have been identified with inhalation of these carcinogens being responsible for around 40% of reported sinonasal malignancies. Foremost among these occupational hazards is exposure to hard woods in the furniture industry. It is thought that biologically active compounds in wood dust impair mucociliary clearance and predispose to carcinogenesis.[4] Acheson et al. reported high rates of nasal cavity and sinus adenocarcinoma in the High Wycombe area and proposed that this was secondary to wood dust exposure.[5] Workers exposed to hard wood have a 70 times increased incidence of sinonasal adenocarcinoma, particularly of the ethmoid sinuses. The UK Government recognizes this as an occupational risk and as such it is a prescribed disease under the 1959 National Insurance Regulations: Reference D6. It remains the duty of a doctor to accordingly inform patients of their rights.

The type of wood is a significant factor. While hardwood exposure increases the risk of developing adenocarcinoma, soft wood exposure is more commonly associated with squamous cell carcinoma (SCC). African mahogany appears to be the most carcinogenic. This wood is often burned by Bantu tribesmen, who have the highest incidence of maxillary sinus cancer in the world. Sinonasal adenocarcinoma that develops in wood-workers has a better prognosis than other nasal adenocarcinomas.[4]

Other occupational hazards include exposure to nickel, which increases risk of developing sinonasal SCC 250-fold. The interval between exposure to nickel and the development of the tumour can be prolonged, with Pedersen et al. reporting a latent interval of between 18 and 36 years.[6] Smoking is also thought to play a role in the development of these tumours, perhaps in a synergistic fashion with wood dust.[4] Other chemicals linked to sinonasal malignancy include chromium, polycyclic hydrocarbons, aflatoxin (found in certain foods and dust), mustard gas and thorotrast (thorium dioxide used in paints for watch dials). Radiation, viral and genetic causes have also been proposed. There is no evidence that chronic sinusitis predisposes to cancer with the incidence of chronic sinusitis in patients with sinonasal malignancies equating to that in the general population.[2]

SURGICAL ANATOMY

The anatomy of the nose and paranasal sinuses is described in detail in Volume 1, Chapter 87, Anatomy of the nose and paranasal sinuses.

General considerations

Sinonasal malignancies spread most commonly by local invasion. The ethmoid and maxillary sinuses are intimately related to the orbit and separated from it by thin bone that is deficient in places to permit the passage of nerves and blood vessels. These anatomical features favour relatively early tumour spread into the orbital contents. The roof of the frontal sinus is similarly thin and this, in combination with perforations in the superior part of the nasal cavity through which the olfactory nerves pass, means that tumours developing at these sites tend to spread intracranially.

In 1933 Öhngren described a line running from the medial canthus of the orbit to the angle of the mandible which he used to separated tumours into two groups, namely those that developed above it and those that developed below it.[7] He suggested that superiorly-based tumours tended to be more aggressive and poorly differentiated, whereas tumours arising inferior to the line were more amenable to treatment and, as a consequence, had a better prognosis. Although this may well be the case, the classification was described before the concept of craniofacial resection was developed. This in combination with the huge advances in radiation oncology that have taken place in the last few decades make Öhngren's suggestion largely of historical interest.

Lymphatic drainage

The lymphatic drainage of the nose and paranasal sinuses is relatively scant. Two lymphatic pathways have been described, the anterior and the posterior. The lymphatics of the anteroinferior part of the nasal cavity and skin of the nasal vestibule drain via the anterior pathway to the first eschelon facial, parotid and submandibular lymph nodes. These in turn drain into the upper deep cervical chain. The remainder of the nose and paranasal sinuses drain through a posterior pathway which runs anterior to the Eustachian tube to first eschelon nodes in the retropharyngeal space and then onwards to the upper deep cervical chain.

PATTERNS OF TUMOUR SPREAD

The advanced stage of tumours at the time of presentation can make their precise origin difficult to determine. Nevertheless, maxillary sinus tumours are the most common (55%) followed by the nasal cavity (35%), ethmoid sinuses (9%) and, rarely, frontal and sphenoid sinuses (1%).

Local invasion

In general, sinonasal carcinomas tend to consume the sinus cavity from which they arise before eroding its bony walls. Periosteum, perichondrium and dura appear to act as a temporary barrier and resist tumour expansion to some extent, a feature possibly explained by the fibroelastic connective tissue component of these tissues.[8] By contrast the bone of the anterior maxilla and orbital floor is very thin and readily destroyed by tumour. Only 25% of maxillary sinus carcinomas are contained within the antrum at the time of presentation.[9] Patterns of local spread are summarized in **Table 7.1**.

Maxillary sinus tumours spread medially from the sinus into the lateral wall of the nasal cavity, laterally into the

TABLE 7.1 Patterns of local spread

Primary site	Anteriorly	Posteriorly	Medially	Laterally	Superiorly	Inferiorly
Frontal sinus	Skin	Anterior cranial fossa, frontal lobes				Ethmoid sinus, nasal cavity
Ethmoid sinus	Skin	Sphenoid, nasopharynx, clivus, pituitary gland	Nasal cavities, cribriform plate	Orbit	Anterior cranial fossa, frontal lobes	Nasal cavity
Maxillary sinus	Cheek, skin	Pterygopalatine fossa, infratemporal fossa, temporal bone, middle cranial fossa	Nasal cavity	Cheek, skin	Orbit	Palate
Sphenoid sinus	Ethmoid sinuses	Clivus, pituitary gland, posterior cranial fossa		Middle cranial fossa, cavernous sinus	Pituitary gland, hypothalamus	Nasopharynx
Nasal cavities	Skin	Sphenoid sinus, nasopharynx		Maxillary sinuses	Anterior cranial fossa, frontal lobes	Palate

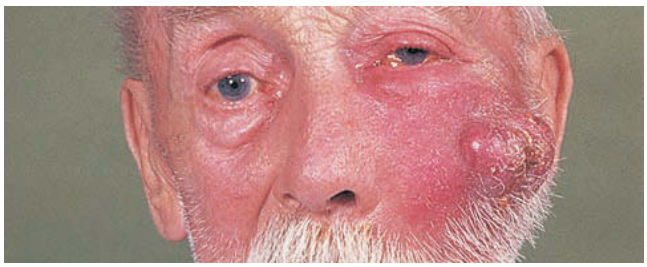


Figure 7.1 An advanced carcinoma of the maxillary antrum. The tumour has breached the lateral wall and presents as a swelling in the cheek.

cheek, superiorly through the inferior orbital fissure into the orbit, inferiorly into the palate and posteriorly into the infratemporal and pterygopalatine fossae (**Figure 7.1**).

Tumours that arise in the ethmoid sinus spread medially into the nasal cavity, laterally into the orbit, superiorly into the anterior cranial fossa and inferiorly into the maxillary sinus (**Figure 7.2**).

Frontal sinus tumours extend through the posterior wall into the anterior cranial fossa and frontal lobes, as well as anteriorly into the skin of the forehead and inferiorly into the nasal cavity. Tumours arising in the sphenoid sinus tend to spread laterally into the cavernous sinus and anteriorly into the ethmoids and nasal cavity (**Figure 7.3**).

Regional spread

Lymphatic spread to regional nodes becomes apparent in 25–35% of patients at some time during the course of their disease. Around 10% of patients present with nodal disease, which is usually a marker of locally-advanced disease. The submandibular and jugulodigastric nodes are the most commonly involved. Bilateral lymph node involvement can occur in patients who develop tumours near the midline.

Distant metastases

Distant metastases at the time of presentation are unusual. They develop in around 20% of patients with adenocarcinomas in contrast to just 10% of those with SCCs.[10] When found they are usually associated with local recurrence.[11]

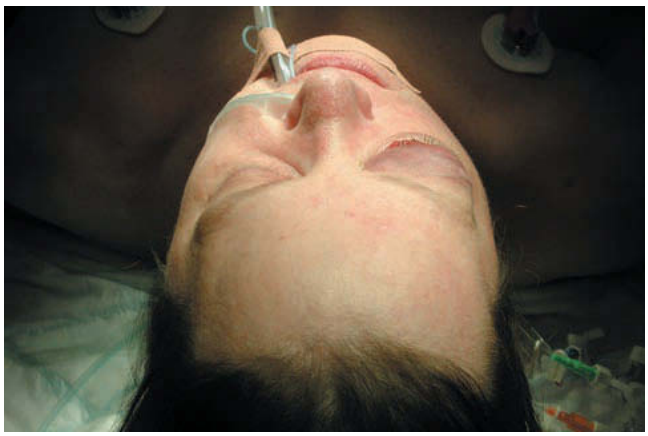


Figure 7.2 An ethmoid carcinoma spreading into the orbit and producing proptosis.

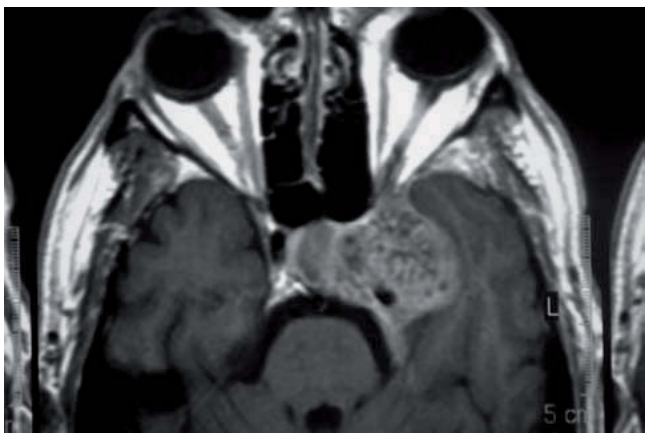


Figure 7.3 MRI of sphenoid tumour that has spread into the cavernous sinus and presented with diplopia secondary to a VIth cranial nerve palsy.

The most common sites for metastases are bone, brain, liver, lung and skin. Unsurprisingly the presence of distant metastases is associated with a poor prognosis except in the small subgroup of patients with metastatic pulmonary adenoid cystic carcinoma (ACC), who can survive for some time if the primary site remains controlled.

STAGING

Staging systems have only been devised for carcinomas of the maxillary sinus, ethmoid sinus and the nasal cavity. These systems are not applicable to mesodermal tumours and have no relevance to olfactory neuroblastoma (OAN) for which separate schemes exist. The TNM classification system for the maxillary sinus (**Figure 7.4**), ethmoid sinus (**Figure 7.5**) and nasal cavity is shown in **Table 7.2**. The staging matrix is presented in **Table 7.3**.[12]

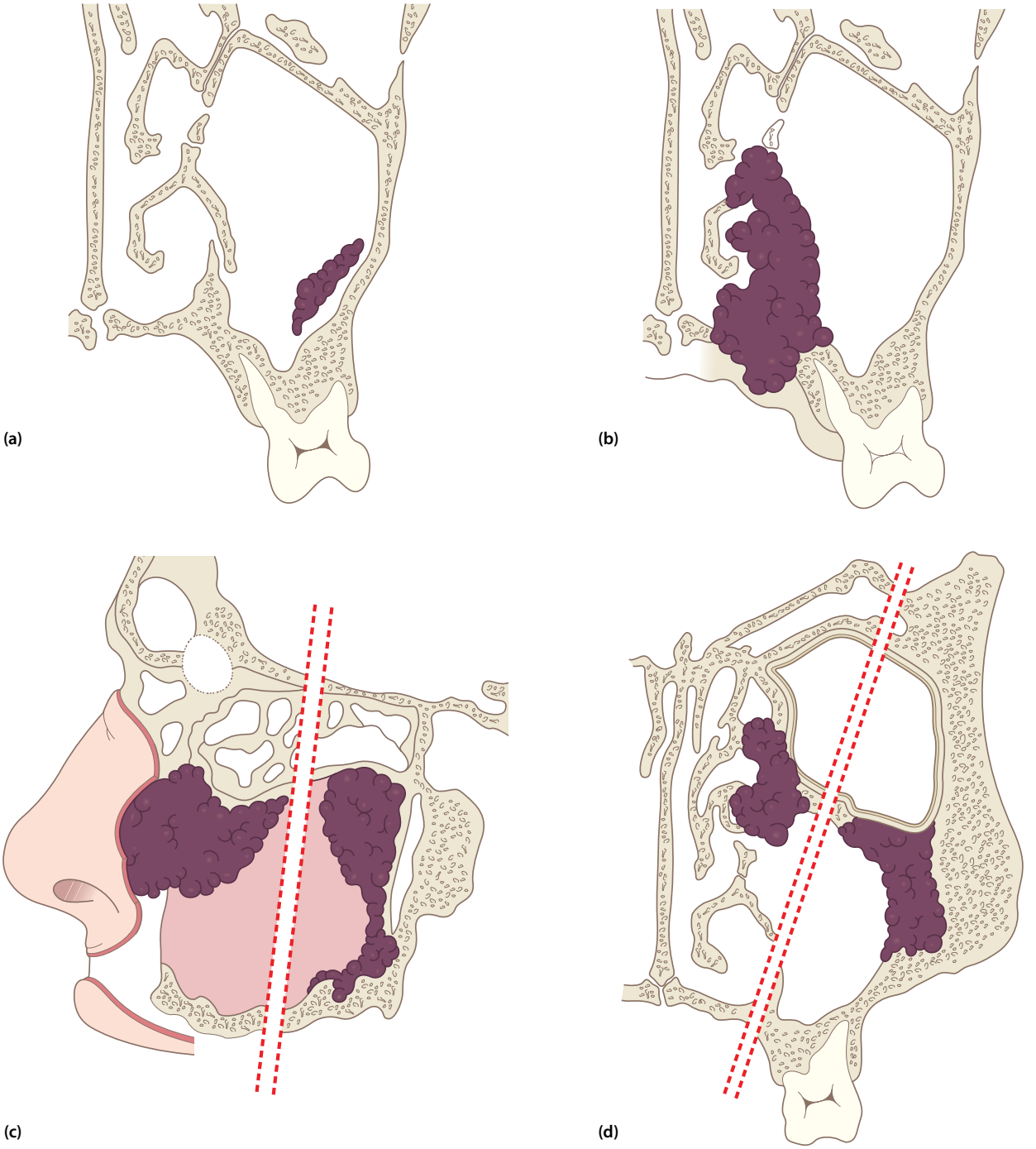
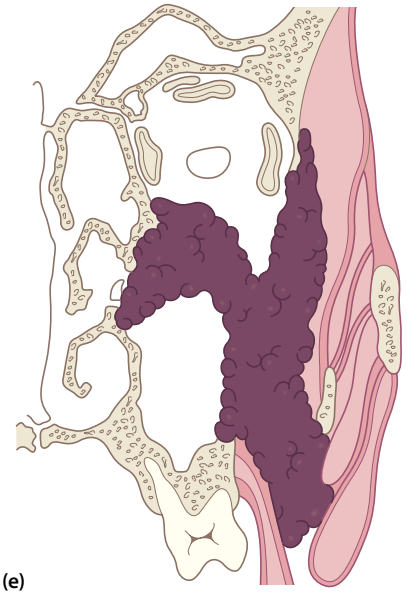
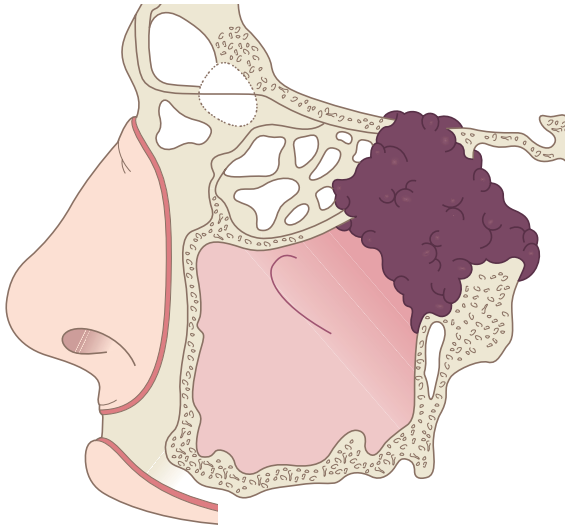


Figure 7.4 TNM diagrams of maxillary sinus carcinoma. **(a)** T1; **(b)** T2; **(c,d)** T3.

(*Continued*)



(e)



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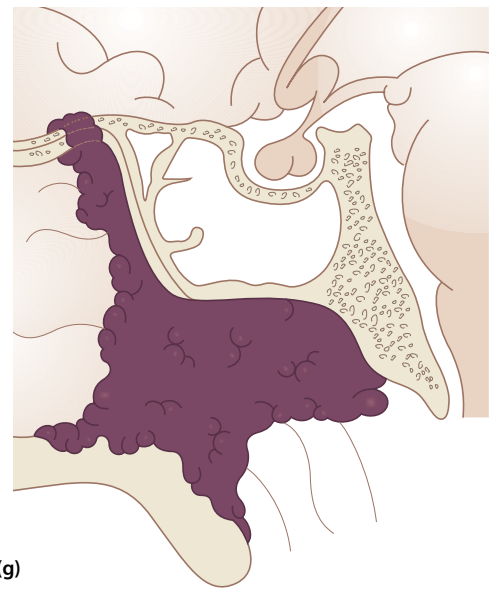


(g)

Figure 7.4 (*Continued*) TNM diagrams of maxillary sinus carcinoma. (e,f,g) T4.

SURGICAL PATHOLOGY

Squamous cell carcinoma

SCC is the most common sinonasal malignancy. The highest incidence is in the seventh decade of life and there is a male preponderance. Most SCCs arise from the lateral wall of the nasal cavity with 50% developing on the turbinates. Two-thirds of septal SCCs are found anteriorly in the region of the mucocutaneous junction. Transformation of Schneiderian papillomas into SCC is a recognized risk. Batsakis reported a 14.6% incidence of SCC in a series of 322 patients with Schneiderian papillomas.[13] Approximately 85% of SCCs are well differentiated tumours. Papillary and exophytic histological patterns are also recognized. It is said that differentiation has little bearing on the ultimate prognosis but this probably reflects the poor overall outcome for these patients and the relative rarity of poorly differentiated forms. Macroscopically some sinonasal SCCs have a polypoid appearance, while others are more obviously fungating, friable and keratinizing.

Adenocarcinoma

Adenocarcinoma accounts for 9% of sinonasal malignancies. Like SCC it too has a male predilection and tends

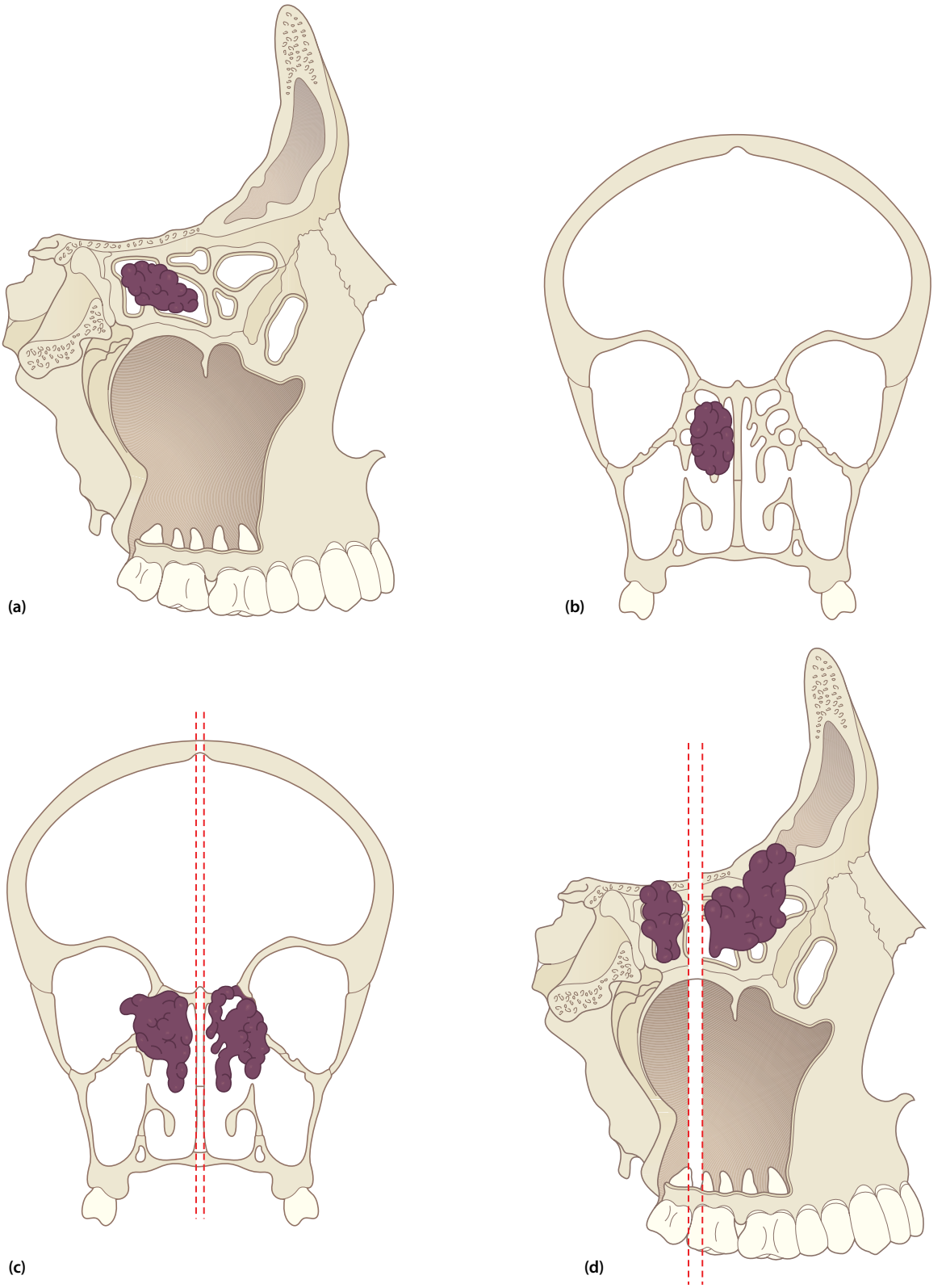
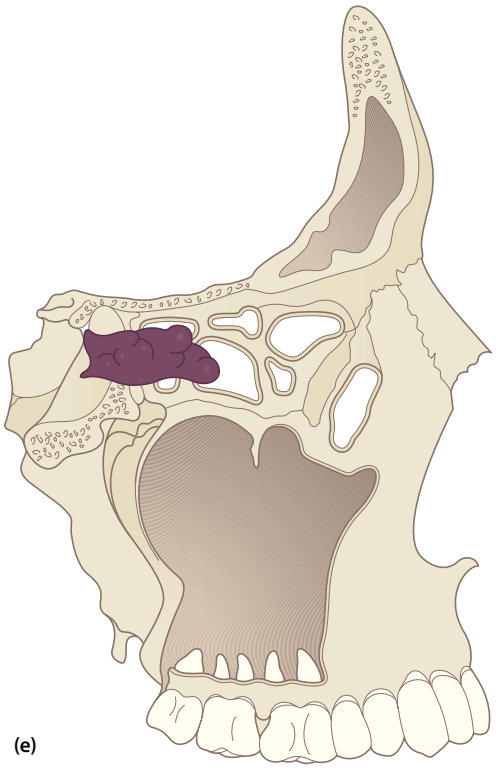


Figure 7.5 TNM diagrams of ethmoid sinus carcinoma. **(a)** T1; **(b)** T2; **(c)** T3; **(d)** T4. (*Continued*)



(e)

Figure 7.5 (*Continued*) TNM diagrams of ethmoid sinus carcinoma. (e) T4.

to affect those in the sixth and seventh decades of life. Adenocarcinomas are generally found in the upper nasal cavity and ethmoid sinuses. They have a slow growth rate and rarely metastasize. Several histological subtypes of sinonasal adenocarcinoma are recognized, namely papillary, sessile, mucoid, neuroendocrine, intestinal and undifferentiated. Papillary adenocarcinomas are the least aggressive form. The intestinal variety is most often associated with woodwork-induced tumours. Sessile and mucoid adenocarcinomas have the worst prognosis.[5]

Adenoid cystic carcinoma

A little less than 5% of sinonasal malignancies are ACCs. As elsewhere ACCs tend to grow slowly but inexorably with early perineurial and vascular spread. All variants of the tumour are seen. The maxillary sinus is the most commonly affected site and patients usually present with a long history of facial pain that can defy diagnosis for many months if not years.

Olfactory neuroblastoma (aesthesioneuroblastoma)

OAN arises from basal cells within the olfactory neuroepithelium. OAN represents less than 5% of all sinonasal malignancies.[14] The incidence of this tumour has a

TABLE 7.2 TNM classification

Stage	Description
Maxillary sinus	
T1	Tumour limited to the antral mucosa with no erosion of bone
T2	Tumour causing bone erosion or destruction, except for the posterior antral wall, including extension into the hard palate and/or middle meatus
T3	Tumour invades any of the following: bone of the posterior wall of the maxillary sinus, subcutaneous tissues, skin, floor or medial wall of the orbit, infratemporal fossa, pterygoid plates, ethmoid sinus
T4a	Tumour invades any of the following: anterior orbital contents, skin of cheek, pterygoid plates, infratemporal fossa, cribriform plate, sphenoid or frontal sinuses
T4b	Tumour invades any of the following: orbital apex, dura, brain, middle cranial fossa, cranial nerves other than the maxillary division of V2, nasopharynx or clivus
Ethmoid sinus	
T1	Tumour confined to ethmoid with or without bone erosion
T2	Tumour extends into the nasal cavity
T3	Tumour extends into the anterior orbit and/or maxillary sinus
T4a	Tumour invades any of the following: anterior orbital contents, skin of the nose or cheek, minimal anterior intracranial extension, pterygoid plates, sphenoid or frontal sinuses
T4b	Tumour invades any of the following: orbital apex, dura, brain, middle cranial fossa, cranial nerves other than V2, nasopharynx or clivus
Nasal cavity[a]	
T1	Tumour involves one subsite
T2	Tumour involves two subsites or ethmoid
T3	Tumour extends into the anterior orbit and/or maxillary sinus
T4a	Tumour invades any of the following: anterior orbital contents, skin of the nose or cheek, minimal anterior intracranial extension, pterygoid plates, sphenoid or frontal sinuses
T4b	Tumour invades any of the following: orbital apex, dura, brain, middle cranial fossa, cranial nerves other than V2, nasopharynx or clivus.

[a] Within the nose, four subsites are recognized, namely septum, floor, lateral wall and vestibule.

TABLE 7.3 Staging matrix

Stage			
0	Tis	N0	M0
I	T1	N0	M0
II	T2	N0	M0
III	T1/2	N1	M0
	T3	N0/1	M0
IVa	T1/2/3	N2	M0
	T4a	N0/1/2	M0
IVb	T4b	Any N	M0
	Any T	N3	M0
IVc	Any T	Any N	M1

bimodal distribution with peaks at 20 and 50 years of age. Unlike most sinonasal malignancies it is more common in women than men. OAN is a neuroendocrine tumour capable of causing paraneoplastic syndromes by secreting peptides. Patients with OAN causing Cushing's syndrome, inappropriate antidiuretic hormone secretion or hypertension produced by vasoactive peptides have been reported in the literature.

OAN is one of a group of 'small round blue cell tumours' and needs to be differentiated from sinonasal undifferentiated carcinoma (SNUC), neuroendocrine tumour, small cell carcinoma, rhabdomyosarcoma and lymphoma. Expert histopathological review is therefore recommended. OAN typically expresses neuroendocrine markers (neurone specific enolase, synaptophysin and chromogranin) and is negative for keratins. S-100 may show positivity around the periphery of the tumour only, helping to differentiate OAN from sinonasal melanoma. Negativity for vimentin, actin and desmin excludes rhabdomyosarcoma.[15]

Hyams et al.[16] developed a four-point histological grading system for OAN based on such features as the degree of differentiation, the tumour architecture, mitotic index, nuclear polymorphism, fibrillary nature of the matrix and tumour necrosis. This tumour can either be extremely aggressive (grade 4) or relatively indolent (grade 1). There are little data for the role of cytogenetics in the diagnosis of OAN.

Survival for more than 20 years is not unusual while others are less fortunate, succumbing to highly aggressive disease with widespread metastases within a few months.[17] Up to 25% of OAN invade the dura and anterior cranial fossa. In 5% of patients metastases to cervical nodes are evident at the time of presentation and distant metastases are already present in around 7% of patients.[17]

OAN can often be predicted from imaging characteristics, based on its location focused on the cribriform plate (**Figure 7.6**).

Disease-specific staging systems have been devised for OAN. The most useful and commonly used systems are those attributed to Kadish et al,[17] Morita et al.[18] and Dulguerov and Calcaterra[19] (**Tables 7.4** and **7.5**).

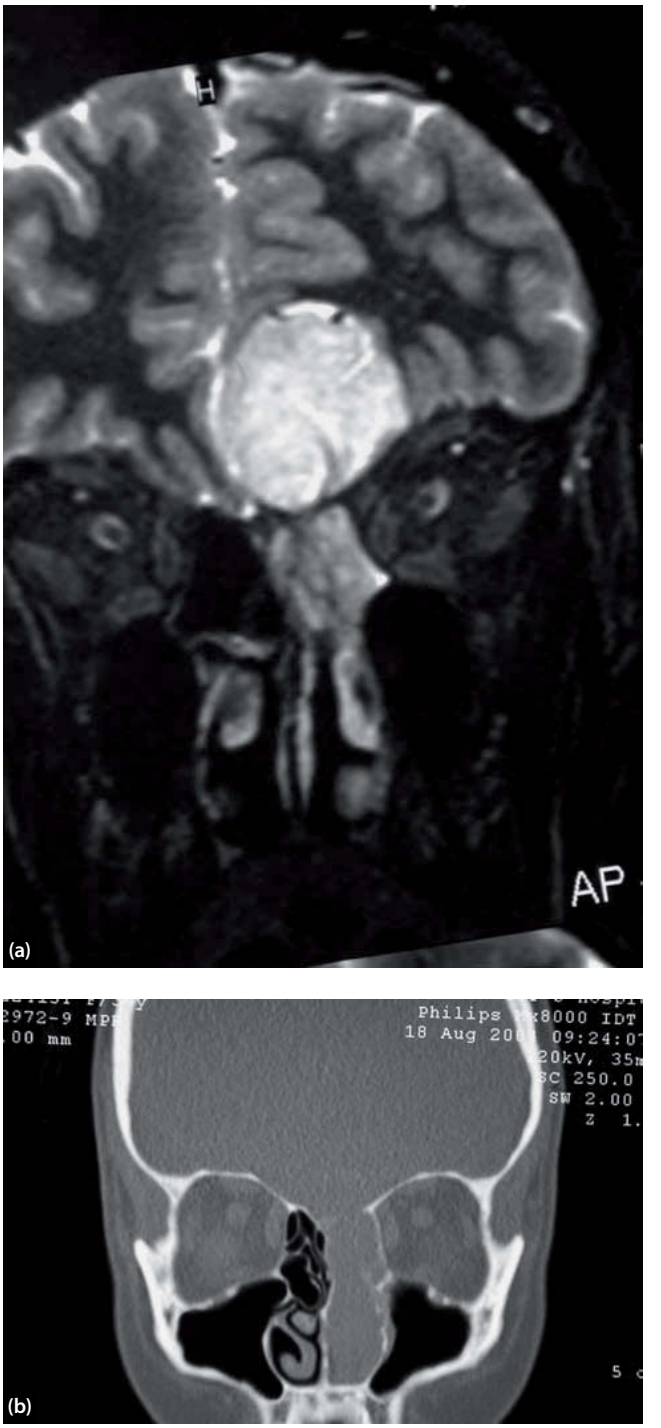


Figure 7.6 (a) MR and (b) CT scan of a patient with a Kadish C olfactory neuroblastoma. The tumour is characteristically centred on the cribriform plate.

TABLE 7.4 Kadish staging system[17] (with Morita's modification)[18]

Stage	Characteristic
A	Limited to nasal cavity
B	Involving nasal cavity and sinuses
C	Extension beyond nasal and paranasal sinuses cavities
D	Tumour with metastasis to cervical nodes or distant sites

TABLE 7.5 Dulguerov staging system[19]

Stage	
T_1	Tumour involving the nasal cavity or paranasal sinuses (excluding the sphenoid sinus) sparing the most superior ethmoidal cells
T_2	Tumour involving the nasal cavity or paranasal sinuses (including the sphenoid sinus) with extension to or erosion of the cribriform plate
T_3	Tumour extending into the orbit or protruding into the anterior cranial fossa without dural invasion
T_4	Tumour involving the brain
N_0	No cervical lymph node metastases
N_1	Any form of cervical lymph node metastases
M_0	No metastases
M_1	Any distant metastases.

Reproduced from Dulguerov et al.[1] with permission.

Sinonasal undifferentiated carcinoma

SNUC was described relatively recently by Frierson et al.[20] It is otherwise known as anaplastic carcinoma and can be hard to distinguish from high-grade OAN. It is a highly aggressive and invasive tumour commonly containing areas of necrosis but, paradoxically, often produces few symptoms despite its extensive nature. Typically SNUC is negative for Epstein–Barr virus, helping to distinguish it from WHO Type 3 nasopharyngeal carcinoma.[21]

Melanoma

Melanoma accounts for 3.6% of all sinonasal malignancies.[22] It is more common in women than men and tends to affect the elderly. The nasal cavity and the septum are usually the sites of origin. Appearances vary from a polypoid mass to an area of ulceration. While some are pigmented, others are not. Immunohistochemistry shows positivity for S100 and HMB-45.[23] Sinonasal melanoma metastasizes less frequently to regional cervical lymph nodes than melanoma that develops elsewhere, but more often to the lungs and brain.[24]

Haemangiopericytomas

These are rare neoplasms that develop from pericytes within the outer capillary wall. They account for less than 5% of all sarcomas. Within the head and neck 20% of all haemangiopericytomas develop in the nasal cavity or sinuses.[25] They have been associated with steroid therapy, coincidental trauma, hypertension and pregnancy. Macroscopically they appear as red-grey, firm, polypoid lesions. Haemangiopericytomas rarely metastasize. Complete surgical excision is necessary as they are relatively radioresistant. There is a 10–60% recurrence rate.

PRESENTATION

Tumours of the nasal cavity cause progressive unilateral stuffiness and blockage, sinus outflow obstruction, bleeding or spot nasal secretions. Distortion of the nose occurs late. The presentation of most sinus malignancies is usually delayed until the sinus of origin is filled with tumour with symptoms being caused by erosion of its walls and extension beyond.

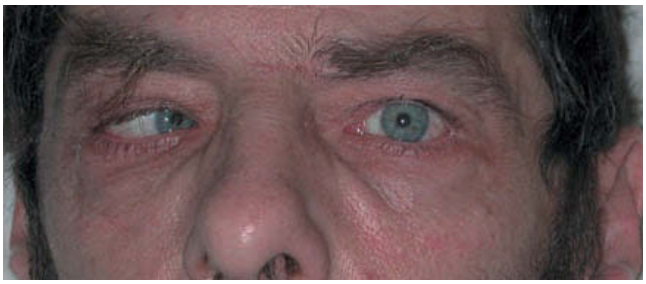


Figure 7.7 Spread of tumour into the cavernous sinus can result in lateral rectus palsy.

Maxillary sinus carcinomas cause facial pain with or without progressive sensory change within the skin of the cheek secondary infiltration of the infraorbital nerve. Erosion of the medial wall is associated with epistaxis and epiphora caused by obstruction of the nasolacrimal duct. Destruction of the posterior wall and spread into the pterygopalatine and infratemporal fossae results in progressive trismus as well as maxillary and mandibular trigeminal nerve deficits. Destruction of bone inferiorly leads to oral masses and teeth mobility. Spread of a tumour superiorly into the orbit gives rise to proptosis and diplopia. A visible swelling or distortion of the cheek develops when tumour breaches the anterolateral wall.

Ethmoid sinus carcinomas usually present with unilateral nasal obstruction and epistaxis. Epiphora, orbital swelling, proptosis or diplopia are not uncommon (**Figure 7.7**). Orbital symptoms and signs also prevail with frontal sinus tumours. Tumours that develop in the sphenoid sinus usually invade the cavernous sinus and infiltrate the contained cranial nerves to produce diplopia and facial pain.

CLINICAL EVALUATION

Endoscopy

A thorough endoscopic examination of the nasal cavity is mandatory in anyone suspected of having a malignancy. While the appearance of some tumours can be obvious with an ulcerative growth others are less conspicuous. It is not unusual for tumours to produce a polypoid reaction in the overlying mucosa. Some of this will be infiltrated but a casual biopsy in the outpatient setting may well be non-diagnostic (**Figure 7.8**).

Imaging

A combination of both computed tomography (CT) and magnetic resonance imaging (MRI) is commonly required for patients with sinonasal malignancies since the former alone may be insufficient for accurate evaluation and staging purposes particularly if it has been adversely affected by amalgam artefact. CT reconstruction gives accurate detail of bone erosion and potential involvement of the skull base. Both axial and coronal views are necessary.

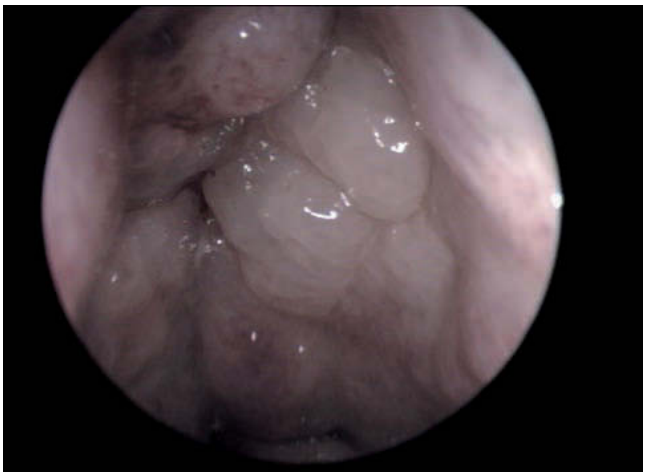


Figure 7.8 Endoscopic view of an extensive SNUC.

Unparalleled information concerning the soft tissue component of tumours is derived from MR imaging. Gadolinum-enhanced MR imaging provides tumour detail that can include flow voids suggesting intense vascularity. It will also detect dural or cerebral infiltration and give an accurate assessment of orbital invasion. T2 and diffusion-weighted sequences are useful in distinguishing between retained secretions, tumour or mucosal thickening (**Figure 7.9**).

Arteriography is rarely required but might be undertaken if pre-operative embolization is being considered to facilitate removal of a vascular tumours such as haemangiopericytoma. FDG positron emission tomography (PET)/CT is not usually necessary for staging the primary tumour but may be helpful in excluding distant disease, for example in melanoma, or in identifying a primary site if there is concern that the disease is metastatic in nature.

Biopsy

Tissue diagnosis is a mandatory part of tumour evaluation. A number of sinus tumours can be excessively vascular and if biopsies are attempted in the outpatient setting facilities should be available to arrest any haemorrhage that might ensue. Biopsies performed under general anaesthesia reduce the rate of non-diagnostic samples and provide the opportunity to sample from within the sinus itself. A Caldwell–Luc approach should be avoided if it is felt this would seed tumour or potentially compromise a subsequent resection (**Figure 7.10**).

TREATMENT

General principles

Malignancies of the nose and paranasal sinuses are rare in contrast to their presenting symptoms. As such many patients still present with advanced disease and there will inevitably be some who are incurable from the outset. Likewise, in some elderly patients concurrent general medical conditions might preclude any major intervention. At initial consultation it is therefore essential that all necessary investigations

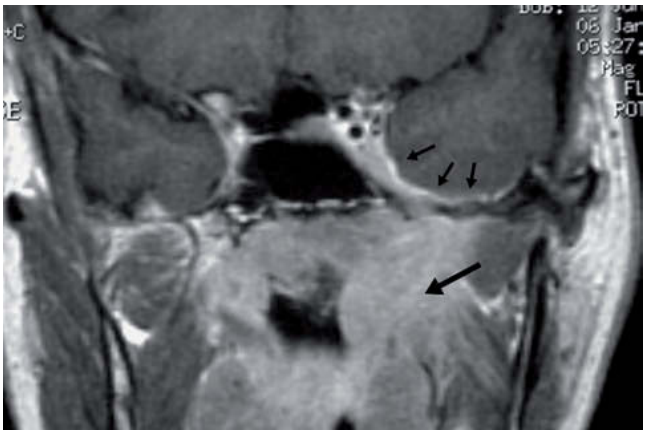


Figure 7.9 MRI and CT scans are complementary and help distinguish between tumour, retained secretions and dural infiltration. This patient had an extensive tumour that had spread into the cavernous sinus, infiltrated the dura of the temporal lobe (small arrows) and the infratemporal fossa (large arrow). The MRI, shown here, shows the true extent of the disease. The spread was not apparent on the CT scan, which had shown a relatively small tumour affecting the sphenoid.

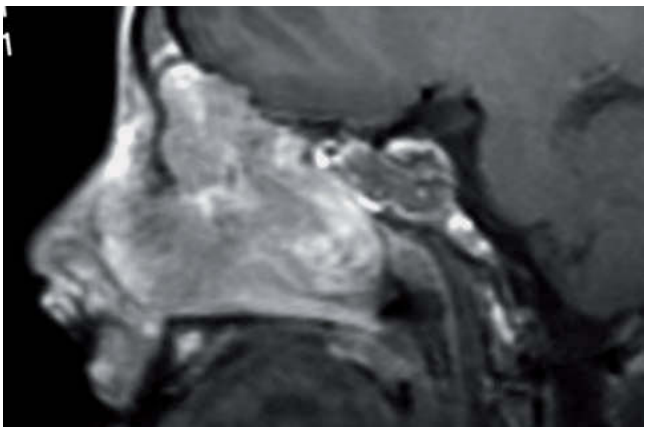


Figure 7.10 This patient lost two litres of blood after a biopsy was taken.

are arranged so that the tumour can be staged accurately and an appropriate treatment plan formulated.

In general, cases should be carefully discussed in a multidisciplinary forum to determine treatment approach and also to facilitate smooth and timely transfer between specialities, so avoiding unnecessary delays in adjuvant therapy. A high quality prosthetic rehabilitation service is an essential component of the MDT. With a palatal resection the defect must be sealed with either an obturator fitted with teeth to restore both speech and normal deglutition or by composite free flap and microvascular techniques. Orbital resections leave an obvious cosmetic deformity but titanium implants have revolutionized the construction and retention of facial prostheses. Radiotherapy is not a contraindication to their use.

There is usually a choice between curative and palliative treatment. In contemplating the latter, it is necessary to balance symptoms and their impact on their life along with the extent of the disease and the potential for distant metastases. Surgery for these patients is both morbid and can raise hopes unrealistically and palliative radiotherapy

might be considered. There are instances, however, when palliative surgery can be useful. Patients with advanced malignant melanoma, for instance, may have a significant reduction in local symptoms with debulking surgery and post-operative radiotherapy. While treatment is likely to be only palliative in patients with large adenoid cystic tumours that have a long natural history, it is often possible to achieve significant periods of good quality survival with local debulking of tumour and adjunctive radiotherapy.

Patients who present early with T1 maxillary tumours may be cured with surgery alone but the majority of patients will require combination therapy. For those patients who are potentially curable most centres recommend a combination of radiotherapy and surgery with the addition of chemotherapy in selected cases. Intensity modulated radiotherapy techniques are generally adopted in order to achieve tumour coverage whilst meeting organ at risk constraints. Post-operative radiotherapy should start within 6 weeks of surgery with 60–65 Gy delivered over 30 fractions. OAN is treated with a combination of surgery and postoperative radiotherapy. Chemotherapy has been used in more advanced cases.[26,27] Multimodality therapy (surgery, radiotherapy and chemotherapy) has generally been demonstrated to be the most effective approach in the treatment of SCC and SNUC.[28–30] The optimal sequencing of those modalities is not clear but if operable surgery followed by post-operative radiotherapy with concomitant platinum-based chemotherapy is the most common approach. In large volume tumours initial non-surgical treatment with (chemo)radiotherapy or chemotherapy alone followed by chemoradiotherapy appears to give better results. Recent evidence based reviews and guidelines support this approach.[31,32] There is increasing experience with proton beam radiotherapy where available, with the possibility of reducing radiation-related morbidity.[33]

There is no role for chemotherapy in the initial treatment of mucosal melanoma, the mainstay of which is surgical resection followed by radiotherapy. In the absence of phase III data it is difficult to draw definitive conclusions regarding the optimal sequencing of treatment modalities in these rare tumours. Topical application of 5-fluorouracil has been advocated by Knegt et al. for adenocarcinoma of the ethmoid sinus.[34]

Other than the stage of disease, patient's wishes and concurrent comorbidity, there are relatively few contraindications to treatment. Local invasion of the anterior cranial fossa and skull base are not necessarily contraindications given the development of modern surgical techniques. Distant metastases confer a poor prognosis and by definition render such patients incurable. Involvement of the facial skin is likewise not a contraindication to treatment and in practice many such patients do well. The involved area is best excised and repaired with either a rotation flap or free flap. Concerns that radiotherapy interferes with healing are less with modern radiotherapeutic regimens.

Surgery for maxillary tumours

A variety of operations has been described, the choice of which is determined by the extent of the tumour and amount of bone that needs to be removed.

PARTIAL MAXILLECTOMY

This entails partial removal of the upper jaw skeleton. Two variants are in common use:

- **medial maxillectomy**, which involves clearance of the lateral wall of the nose including the ethmoid sinuses
- **palatal resection** along with the adjacent alveolus, which is used for tumours of the oral cavity that involve the hard palate. In its simplest form this is called a fenestration although this term is technically incorrect since palatal fenestration was originally described for placing radium implants into the cavity of the antrum. Most partial maxillectomy defects are nowadays reconstructed with free flaps, but for some patients there is still some advantage with the less sophisticated procedure of obturation since this obviates a donor site and allows visualization of the treated cavity during surveillance for recurrence.

TOTAL MAXILLECTOMY

This entails the total removal of the upper jaw, preferably as a bony box containing the tumour.

EXTENDED MAXILLECTOMY

An extended maxillectomy is required when the tumour extends beyond the upper jaw. If this involves the skull base the term craniofacial resection is used.

Surgical approaches

To facilitate the various bony resections it is necessary to use the appropriate soft tissue access procedure, of which three are commonly described:

- **Lateral rhinotomy**. Although this approach is usually attributed to Moure[35] it was originally described by Michaux[36] some 50 years earlier in 1854. It gives excellent exposure of both the nasal cavities and medial maxilla with a cosmetically acceptable incision in the lateral nasal crease (**Figure 7.11**).

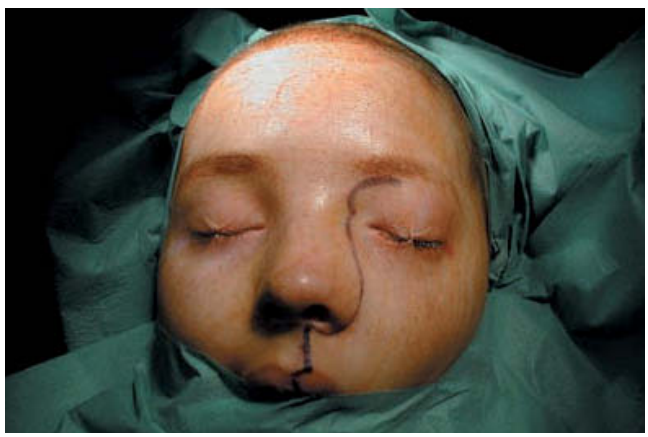


Figure 7.11 Extended lateral rhinotomy incision to include the lip. In most cases division of the lip to gain additional lateral exposure is unnecessary.

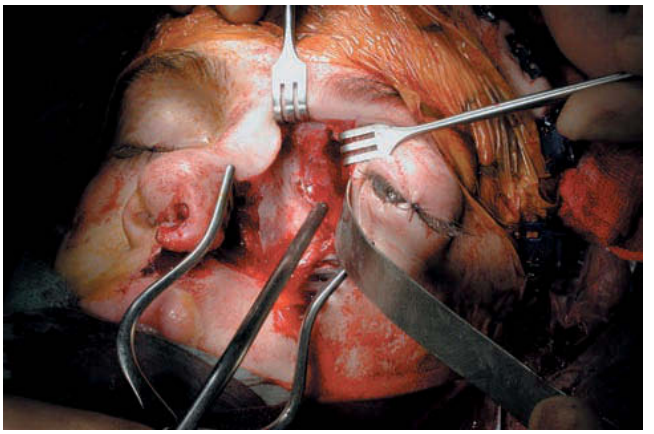


Figure 7.12 Weber–Fergusson incision.

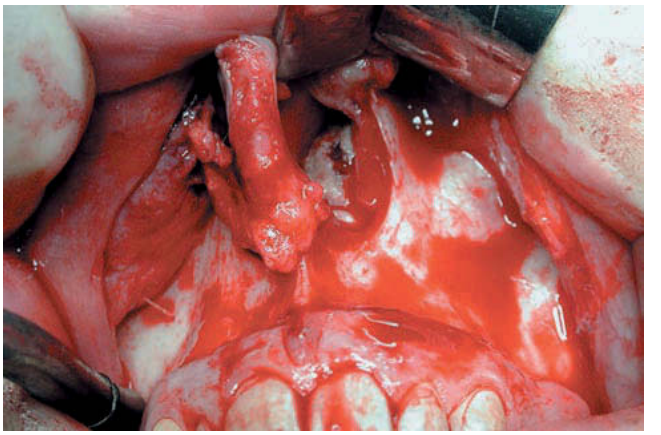


Figure 7.13 Midface degloving exposure.

- **Weber–Fergusson**. This approach is incorrectly attributed to both Fergusson and Weber and was instead originally described by Gensoul in 1833 (**Figure 7.12**).
- **Midfacial degloving**. Casson et al.[37] described the addition of intercartilaginous incisions to the sublabial incisions advocated by Converse[38] to allow elevation of the soft tissues of the midface. This has been popularized in the UK and well described by Howard.[39] The sublabial incisions should extend from maxillary tuberosity to the contralateral tuberosity to gain maximum exposure. The soft tissues of the cheek are elevated in the subperiosteal plane to the infraorbital nerves. Incisions into the nasal fossa are then made along the piriform aperture on both sides. Bilateral intercartilagenous incisions are extended to a transfixion incision and the skin elevated over the dorsum of the nose using standard rhinoplasty techniques. The incisions are then connected to allow complete elevation of the midface to the infraorbital nerves and medial canthi. With division of the infraorbital nerve the whole of the anterior face of the maxilla to the inferior orbital rim can be exposed. Relevant osteotomies permit varying degrees of maxillectomy. As well as access to the maxilla, pterygopalatine fossa and nasal fossa midface degloving can give wide access to the central skull base and with a Le Fort I osteotomy can be extended to allow better access to the clivus (**Figure 7.13**).[40, 41] The selection of the specific approach depends on the pre-operative assessment, but generally if the anterior ethmoids, frontonasal duct, orbit or zygoma is involved a different approach is indicated. In most other tumours a lateral rhinotomy or midfacial degloving approach will usually give good access for medial maxillectomy and requires little rehabilitation. Extensive tumours require some form of craniofacial approach.

ANAESTHESIA

Skilled anaesthesia is essential. Topical anaesthesia of the nasal mucosa with a decongestant solution along with hypotensive general anaesthesia are of considerable benefit to the surgeon. An oral tube (or tracheostomy) is required for a midfacial degloving.

Maxillectomy

SOFT TISSUE APPROACH

The maxilla is best exposed by the Weber–Fergusson incision. The transverse limb should be placed close to the lid margin to maintain cosmesis, commonly in the first crease. Any lateral extension into a crow's foot should likewise run in an inferolateral direction to minimize post-operative oedema. In the medial canthal region, where the potential for skin loss as a result of radiotherapy is greatest, it is helpful to curve the incision forward over the nasal bones for additional support. An incision along the crest of the philtrum and stepped on the lip is more acceptable than a midline incision. The mucosal incision along the midline of the hard palate turns laterally at the junction with the soft palate passing behind the maxillary tuberosity and then round the alveolus anteriorly. The facial skin flap is raised in a submuscular plane and all the soft tissue incisions are gently dissected free of the bone to allow the subsequent osteotomies (**Figure 7.14**).

OSTEOTOMIES

The body of the zygoma, midline of the palate and pterygoid plates need to be divided. The palatal osteotomy is placed in the floor of the nasal cavity and is most easily carried out using power tools. The pterygoid plates are best separated from the maxilla with a curved osteotome and subsequently dissected free from the muscles. Osteotomies are made medially through the ethmoid cells and then frontal process of the maxilla, the latter after dividing the lacrimal sac. The maxilla is separate from the skull above by osteotomies through the frontal process of the maxilla. Laterally the osteotomy is made through the body of the zygoma. In tumours that are laterally placed, and in which the zygoma needs to be included in the resection then the osteotomy is best made in the lateral orbital wall below Whitnall's tubercle and through the zygomatic arch (**Figure 7.15**).

The remaining bony attachments in the posterior ethmoid cells and antral roof break readily on mobilizing the maxilla. Soft tissue remnants are then divided with Mayo scissors and the maxilla removed. Bleeding from the internal maxillary artery is controlled by packing,

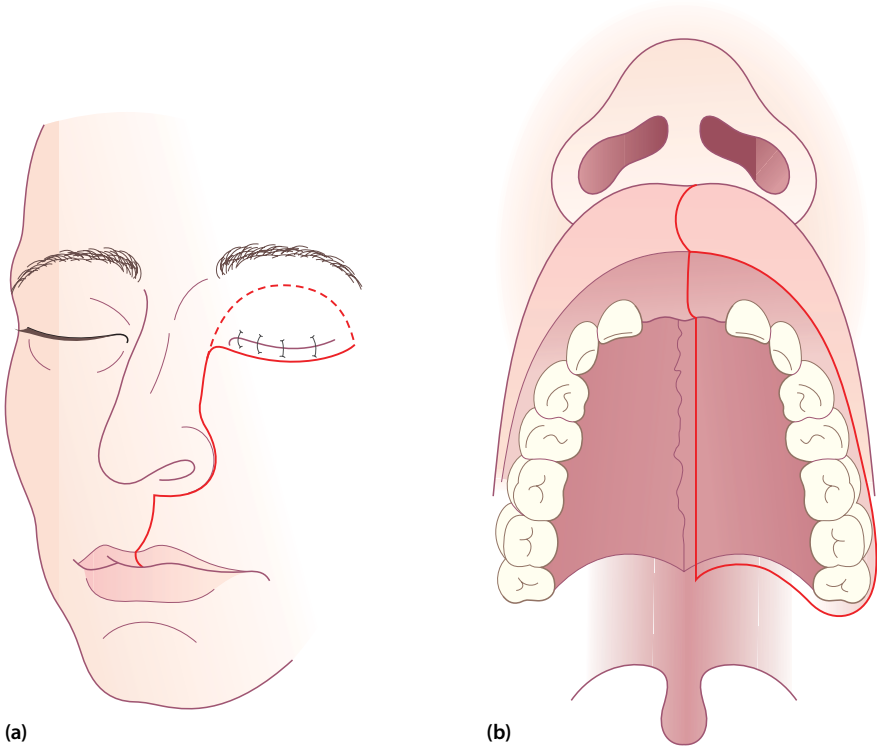


Figure 7.14 Classic maxillectomy. **(a)** Weber–Fergusson incision; **(b)** palatal incision.

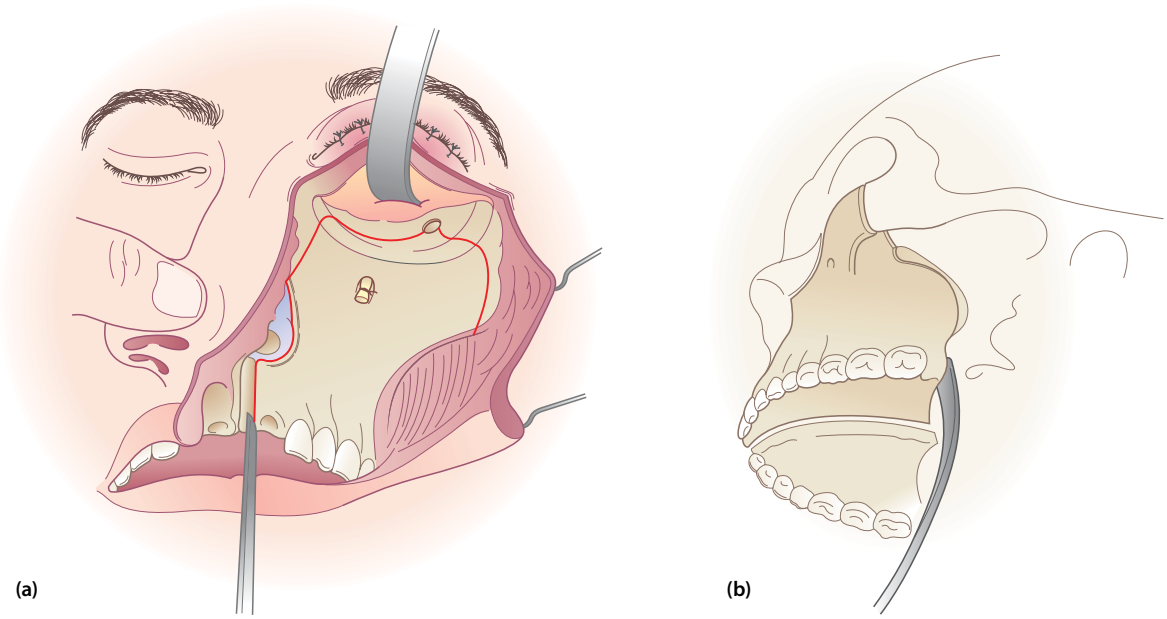


Figure 7.15 Classical maxillectomy. **(a)** Following the elevation of the facial flap, the maxilla is freed with osteotomies through the zygoma, palate and frontal process of the maxilla; **(b)** freeing the pterygoid plates.

Ligaclip application, diathermy or haemostatic matrices, are often used in combination.

COMPLETION OF THE RESECTION

Following removal of the maxilla, further tissue removal is often necessary to promote drainage from the remaining sinuses. The ethmoid cells should be exenterated completely and both the sphenoid and frontal sinuses opened widely. If there is obvious involvement of the orbital periosteum then exenteration is generally indicated. The support of the globe is complex and virtually all the medial and inferior orbital walls can be removed without enopthalmus developing. However, the removal of Whitnall's tubercle laterally results in lack of support for the eye, which can be corrected by transposing the temporalis muscle medially. Orbital exenteration is achieved by an extraperiosteal dissection and transection of the muscle cone at the apex with

Mayo scissors. Bleeding from the ophthalmic artery can be stopped by applying local pressure or bipolar coagulation. Following orbital exenteration the eyelids are preserved but the lid margins and tarsal plates sacrificed, so producing a smooth skin-lined cavity onto which an onlay prosthesis can be fitted.

NECK DISSECTION

Some controversy remains about management of the neck in SCC of the paranasal sinuses. Unlike the plethora of information that exists regarding elective neck dissection in other head and neck sites there are few reports of the use of elective selective neck dissection for management of the maxillary sinus. The rate of occult metastasis is less than 10% with no suggestion in retrospective reviews that elective selective neck dissection contributes to an improved rate of neck control or overall survival.[42]

RECONSTRUCTION AND REHABILITATION

Patients requiring midface reconstruction for malignant disease have undergone extensive ablative surgery and most will require post-operative radiotherapy. This type of facial reconstruction attracts controversy not only because of the many reconstructive options available but also because dental and facial prostheses can be successful in selected cases. Careful rehabilitation, be it biological or prosthetic, aims to ensure a good cosmetic and functional outcome with separation of the nasal and oral cavities.[43, 44]

Low defects not involving the orbital adnexae can often be successfully treated with dental obturators. For the more extensive maxillary defects there is consensus that a free flap is required. Composite flaps of bone and muscle harvested from the iliac crest with internal oblique or the scapula tip with latissimus dorsi can more reliably support the orbit and cheek than soft-tissue free flaps and non-vascularized grafts, and also enable an implant-borne dental or orbital prosthesis. Nasomaxillary defects usually require bone to augment the loss of the nasal bones, but orbitomaxillary cases can be managed more simply with local or soft-tissue free flaps.

In cases where a dental obturator is used, healing of the bony cavity can be rapid but it is advantageous to apply a split-skin graft to the under surface of the facial skin flap. After resuturing the facial incision, the cavity should be immediately fitted with a temporary prosthesis to cover the palate and restore normal facial contours. The prosthesis can be secured with either circumzygomatic wires attached to cleats or more simply fixation screws inserted into any remaining aspect of the hard palate. This primary prosthesis is changed after some 14 days and appropriate adjustments made. This process is repeated several times over the subsequent weeks until such time as it is judged that the cavity has healed and a final prosthesis can be constructed.

Medial maxillectomy using the lateral rhinotomy approach

This approach gives good access to the nasal cavities, the ethmoids, nasopharynx, sphenoid and the pterygopalatine fossa (**Figure 7.16**). For more extensive tumours an en bloc resection can be achieved by combination with an anterior craniofacial approach. The incision is cosmetically acceptable as it passes along the lateral border of the nose to the upper edge of the alar margin. For more extensive resections the incision can be continued into the nasal cavity without compromising the final cosmetic outcome. The upper end should start just above the level of the medial canthus. The orbital periosteum is elevated as for an external ethmoidectomy and extended laterally over the maxilla to the infraorbital nerve. The lacrimal sac and duct are exposed by removing the overlying bone. The orbital contents can then be completely freed medially by dividing the sac low down, clipping and dividing the anterior ethmoidal artery and also by freeing the insertion of the trochlea by sharp dissection. Access to the nasal cavities, ethmoids and antrum is achieved by extending the bony window as required with little cosmetic defect. The mucosa of the nose, antrum and ethmoids can be resected along with the entire lateral nasal wall. The view obtained following the removal of this main block of tissue is excellent and the resection can be extended into the sphenoid and frontal sinuses or alternatively into the pterygopalatine fossa. Packing is rarely required after resection.

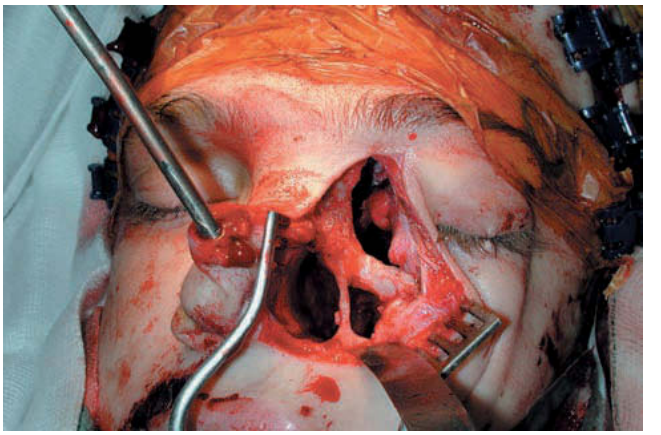


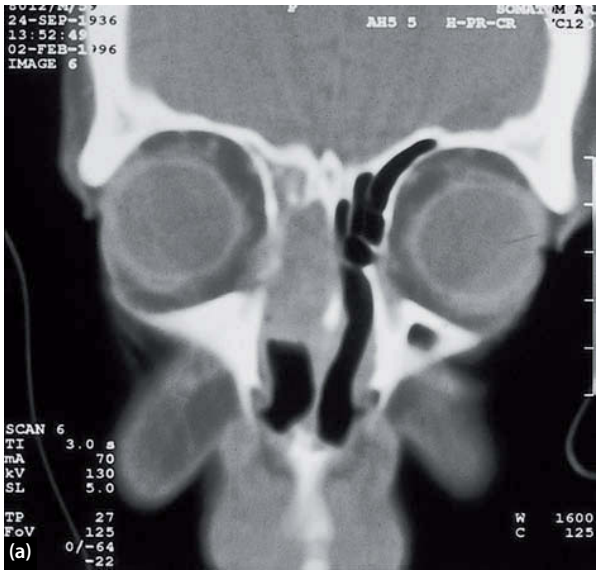
Figure 7.16 Medial maxillectomy approach used to remove a tumour of the ethmoid.

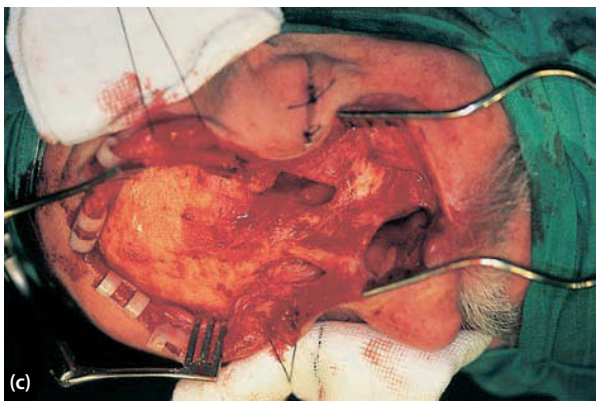
This sort of resection can also be obtained using an entirely endoscopic approach utilizing the appropriate drills and debriders (see below).

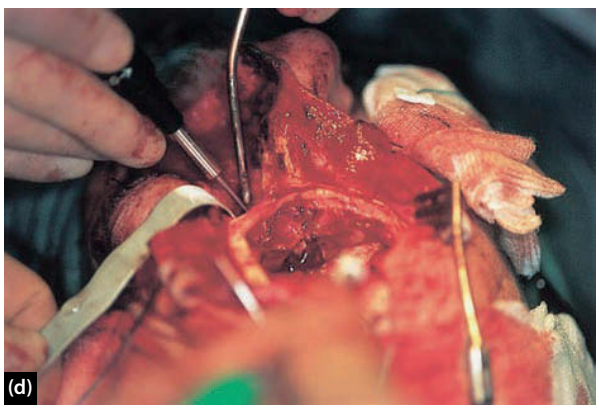
Surgery for ethmoidal tumours

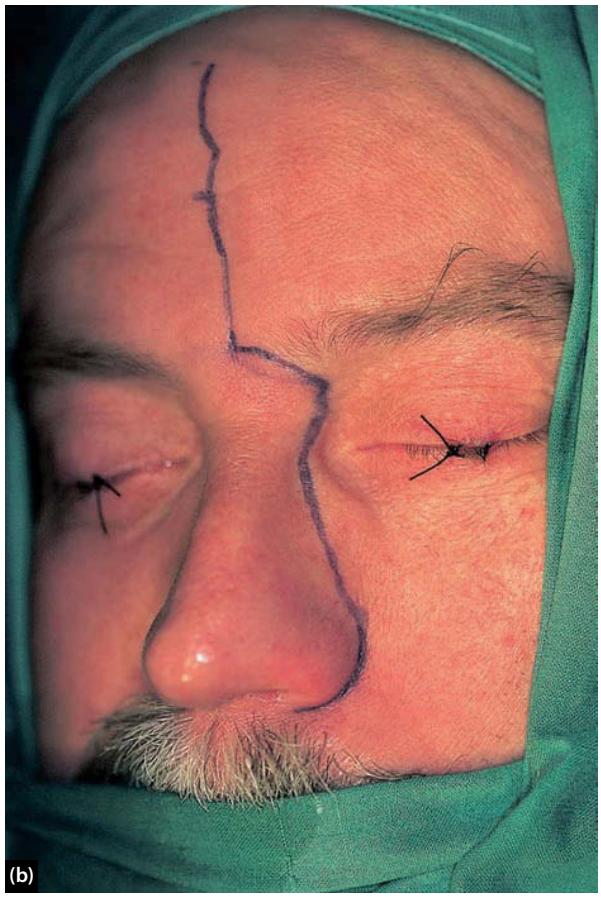
Involvement of the cribriform plate region was recognized as one of the major reasons for failure to control ethmoid neoplasms with some of the above approaches. Ketcham et al,[45] Clifford[46] and Cheesman et al.[47] (**Figure 7.17**) described a combined intracranial and transfacial approach that controls and allows resection of tumours involving the cribriform plates, dura and even some tumours invading the frontal lobes. The appropriate selection of approach has been best summarized by Cheesman and Reddy,[48] who subclassified the craniofacial procedures into three types:

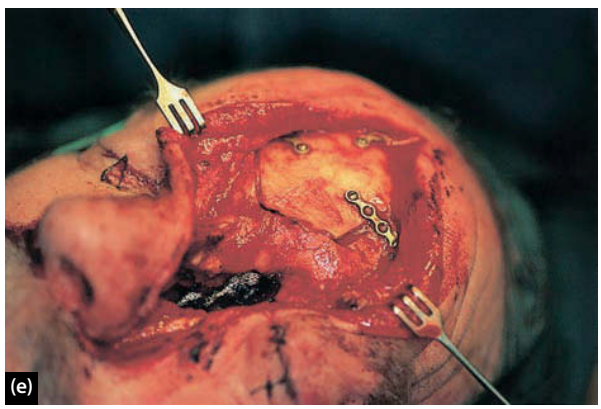
- **Type 1: craniofacial (transorbital) resection.** This procedure is essentially an extended medial maxillectomy using a lateral rhinotomy incision. The operation entails careful











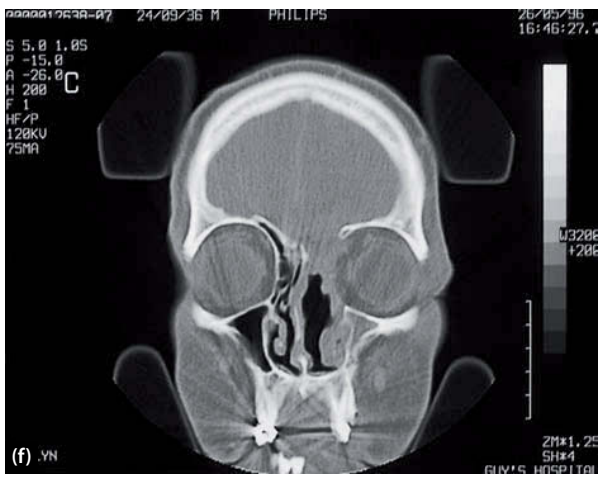


Figure 7.17 Stages of an anterior craniofacial resection.
(a) pre-operative CT acquired face down; **(b–e)** resection; **(f)** post-operative CT.

exploration of the anterior nasal cavities using the operating microscope and frozen section control. The wide exposure allows resection and repair of both the ethmoid roof and orbital periosteum if indicated. A similar approach has been described by Draf and Samii.[49]

- **Type 2: craniofacial (window craniotomy) resection**. In this procedure a lateral rhinotomy approach is used for anterior access and a bicoronal incision utilized to provide a pericranial flap and access to the frontal bone. A small midline 'window' craniotomy usually utilizing the frontal sinus is made giving access to the floor of the anterior cranial fossa. The dura is elevated from the roof of the ethmoids and cribriform plate and the area is encompassed with a cranial osteotomy. This osteotomy, in conjunction with those of the lateral rhinotomy, allows the en bloc resection of both ethmoid complexes. Involved dura and olfactory bulbs can be excised and repaired with fascia lata and pericranium. The window bone flap is replaced and fixed with miniplates. Following soft tissue closure, remarkably little cosmetic defect is evident. The combined approach not only gives excellent visualization of the ethmoid region but also readily allows extensions of the resection into the sphenoid, orbit, pterygopalatine fossae and central skull base.
- **Type 3: craniofacial resection**. This operation is performed in conjunction with a neurosurgeon and combines a transfacial approach with a neurosurgical approach, such as a frontolateral craniotomy, to allow the resection of extensive tumours (**Figure 7.18**). Skull base surgery demands an interdisciplinary approach.

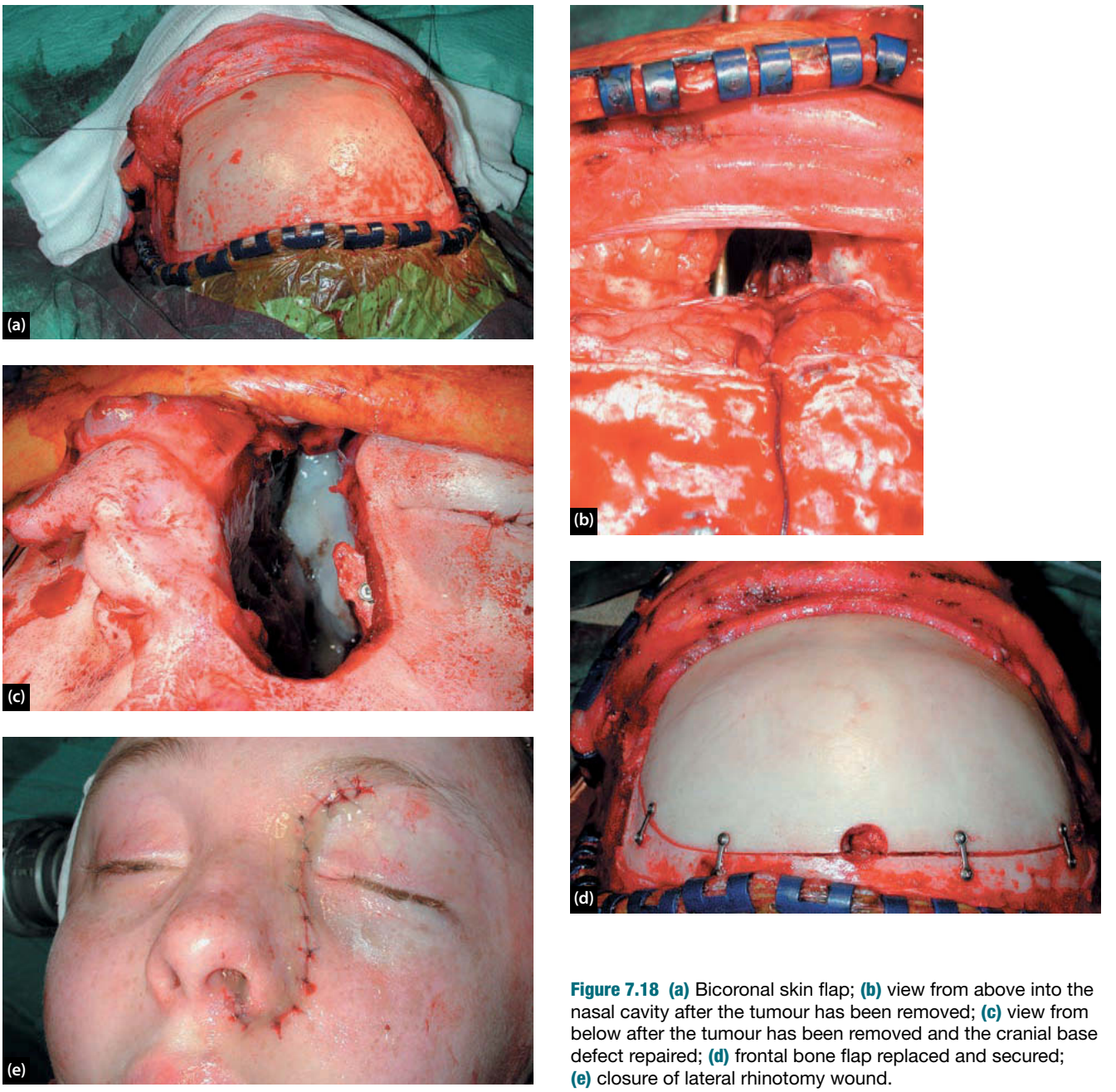


Figure 7.18 **(a)** Bicoronal skin flap; **(b)** view from above into the nasal cavity after the tumour has been removed; **(c)** view from below after the tumour has been removed and the cranial base defect repaired; **(d)** frontal bone flap replaced and secured; **(e)** closure of lateral rhinotomy wound.

There is a trend nowadays for the otorhinolaryngologist to use endoscopic techniques in order to guide the neurosurgeon's osteotomies from below.

Many tumours suitable for Type 1 craniofacial resections can now be approached with endoscopic techniques and extensive tumours requiring a type 3 approach might often be deemed incurable.

Endonasal endoscopic approaches

The introduction and rapid expansion of endoscopic surgery for inflammatory conditions of the sinuses in the 1980s was followed by the extension of these techniques to the skull base and tumour surgery.[50–53] Tumour debulking is usually necessary along with some septal resection for access. The involved sinuses are widely exposed and all bone adjacent to the tumour removed. Resection can continue to include orbital periosteum, dura, crista galli and olfactory bulbs as necessary. Dissection involves drills, debriders and bipolar diathermy as well as standard endoscopic sinus instruments. Neuronavigation and sometimes ultrasonic aspiration are also required especially for intracranial extension. Careful endoscopic repair of dural defects and orbital periosteum with septal mucosal flaps, fascia lata or temporalis fascia complete the procedure. Involvement of the nasal bones, frontal sinus, dura lateral to the ethmoidal roof and orbital contents are contraindications to endoscopic approaches although these may also be combined with transcranial approaches or orbital exenteration where appropriate. A much more detailed treatment of endoscopic resections of sinus tumours is available in Volume 1, Chapter 114, Endoscopic management of sinonasal tumours.

Management of the orbit

Attempts to preserve the orbital contents and reduce mutilation often result in orbital recurrence. If the orbital muscles, globe or orbital apex are involved a lid sparing exenteration is required. The lids provide good skin cover of the defect and can also be used to cover osseointegrated implants, which can be placed at the time of the surgery. However, the orbital periosteum may be involved with tumour while the underlying fat and orbital contents are not, and the use of peri-operative frozen section can determine those patients whose orbits can be safely retained. If frozen section confirms tumour has not penetrated the periosteum it can be resected and repaired without adversely affecting outcome.[54, 55] Orbital involvement despite exenteration significantly affects survival.[56]

PROGNOSIS

The overall prognosis of sinonasal malignancy is directly related to the degree of local control.[1] Absolute local control rates for all malignancies are 50% at 5 years, 31% at 10 years and 21% at 15 years.[57]

Prognosis varies very significantly for different pathologies, however, with very high 5-year survival rates for OAN and ACC and extremely poor prognosis for SNUC and malignant melanoma. For the first two diagnoses in particular, patients may continue to develop relapses for several decades after treatment. In the Memorial Sloan Kettering Cancer Centre series of 166 patients undergoing anterior skull base resection, patients who did experience a recurrence were most likely to fail locally (66.7%). Distant metastases (46.4%) and regional failures were less common (16.7%).[58] Factors associated with prognosis are shown in **Table 7.6**.

TABLE 7.6 Factors affecting prognosis

Factor	Percentage
Anatomical factors: location[1]	
Nasal cavity	77
Maxillary sinus	62
Ethmoid sinus	48
Above Ohngren's line	Worse prognosis
Pathological factors: histological type[39]	
OAN	88
Adenocarcinoma	68
SCC	51
Undifferentiated carcinoma	44
Mucosal melanoma	18
Tumour stage[1]	
T_1	91
T_2	64
T_3	72
T_4	49

5-year actuarial survival.

BEST CLINICAL PRACTICE

- ✓ A combination of CT and MRI scans should be acquired as part of the staging and planning process. These imaging techniques provide complementary information on bone erosion, dural, brain and orbital invasion.
- ✓ Biopsy is most appropriately obtained using endoscopic techniques.

FUTURE RESEARCH

- What is the most appropriate treatment for SCC and SNUC? Are the results for neoadjuvant chemoradiotherapy better than the traditional approach of surgery followed by radiotherapy? Does the addition of chemotherapy improve survival or just add morbidity? Which regimen is optimal? Should the surgical margins incorporate the initial extent of the tumour or just that remaining after chemoradiotherapy?
- Management of the N_0 neck has yet to be determined. Should only N_+ disease be treated or should patients with advanced (T_{3-4}) N_0 tumours also undergo treatment of the neck? Should all histopathological subtypes receive treatment of the N_0 neck or just SCC and OAN? Which levels should be dissected – levels I-III, I-IV or I-V dissection?
- What is the role of surgery for palliation in incurable disease? Is it really justified?
- In reconstruction of the midface, when should an obturator be used and when is a free composite flap appropriate?

KEY POINTS

- Sinonasal malignancies can be difficult to differentiate from non-neoplastic lesions.
- Sinonasal malignancies are uncommon, representing <1% of all malignancies and <3% of all upper aerodigestive tract cancers.
- A large number of sinonasal malignancies are caused by inhaled carcinogens. Risk factors include:
  - wood dust
  - nickel
  - chrome
  - polycyclic hydrocarbons
  - aflatoxin
  - mustard gas
  - thorotrast.
- Maxillary sinus tumours are the most common (55% of all sinonasal malignancies), followed by nasal cavities (35%), ethmoid sinuses (9%) and rarely frontal and sphenoid sinuses (1%).
- Sinonasal malignancies tend to present late.
- The main treatment modalities are surgery and radiotherapy.
- Chemoradiotherapy followed by surgery is advocated for SNUC and advanced ethmoidal SCC.
- Contraindications to aggressive treatment are spread to the sphenoid sinus, middle cranial fossa, optic chiasma, cavernous sinus or prevertebral fascia, as well as the presence of distant intracranial or systemic metastases.
- The prognosis of sinonasal malignancies has improved over the past three decades, but remains poor overall, and is directly related to the degree of local control.
- Absolute local control rates for all malignancies are 50% at 5 years and 31% at 10 years.
- Olfactory neuroblastoma and adenoic cystic carcinoma may relapse after a decade and thus patients should be followed up for at least 15 years

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CHAPTER 8

NASOPHARYNGEAL CARCINOMA

Raymond King-Yin Tsang and Dora Lai-Wan Kwong

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SEARCH STRATEGY

Apart from the standard textbooks on nasopharyngeal carcinoma, the data in this chapter are based on a Medline search using nasopharyngeal carcinoma against the following keywords: diagnosis, pathology, immunology, treatment and complications.

INTRODUCTION

The nasopharynx is situated deep inside the head and the carcinoma arising in the epithelium of the nasopharynx has a different aetiology, epidemiology and biology compared to other cancers of the upper aerodigestive tract. The deep location of the nasopharynx and the wide spectrum of presenting symptoms make early diagnosis difficult. The distinct tumour biology requires different staging and treatment paradigms compared to other head and neck cancers. Nasopharyngeal carcinoma has been called an enigmatic tumour.[1]

APPLIED ANATOMY

The nasopharynx is the most superior part of the pharynx with the inferior border defined as the lower level of the soft palate. Anteriorly it connects to the nasal cavities through the posterior choana. Superiorly the roof of the nasopharynx is formed by the floor of the sphenoid sinus and slopes down to become the posterior wall, which is formed by the clivus bone. The inferior outlet normally opens into the oropharynx but is closed by the soft palate during swallowing and phonation. The cartilaginous Eustachian tubes on both sides open on the lateral wall of the nasopharynx. A recess extends postero-laterally on both sides of the posterior wall of the nasopharynx to form the lateral recess of the nasopharynx, also known as the fossa of Rosenmüller. The depth of the fossa of Rosenmüller is variable. The posterior cushion of the Eustachian tube opening forms the anterior wall of the fossa of Rosenmüller. Most early stage nasopharyngeal primaries originating from the fossa of Rosenmüller are difficult to detect unless the area is carefully inspected during endoscopy.[2] Cancers arising from the fossa of Rosenmüller therefore frequently invade the Eustachian tube and affect function, leading to the development of otological symptoms.

The nasopharynx is covered with pseudostratified squamous epithelium similar to the mucosa of the nasal cavities and paranasal sinuses. The second layer is the muscular layer formed by the superior constrictor muscles. At the upper part of the clivus and roof, the nasopharynx, the superior constrictor is absent. The pharyngobasilar fascia forms the outermost layer of the nasopharynx wall. The pharyngobasilar fascia anteriorly attaches to the medial

pterygoid plates on both sides. Except for the pterygoid plates in the anterior part of the lateral nasopharynx, the lateral walls of the nasopharynx are devoid of bone. Immediately lateral to the pharyngobasilar fascia are the parapharyngeal spaces with the fat pads and muscles of the soft palate (levator palatini, tensor veli palatini and salpingopharyngeus) on both sides. Cancer of the nasopharynx readily spreads to the ipsilateral parapharyngeal space. Just anterior to the posterior choana, in the posterior part of the lateral nasal wall, is the sphenopalatine foramen. Cancers from the lateral wall can spread to the pterygopalatine fossa via the sphenopalatine foramen. From the pterygopalatine foramen, the cancer then spreads along the foramen rotundum and into the cavernous sinus intracranially, producing ophthalmoplegia. The floor of the sphenoid that forms the anterior part of the roof of the nasopharynx is thin and cancer can easily spread into the sphenoid sinus. From the sphenoid sinus, the cancer can then spread into the orbital apex and cause eye symptoms.

There is extensive lymphatic drainage to both sides of the neck from the nasopharynx. The first echelon of lymphatic drainage is the retropharyngeal lymph nodes (nodes of Rouvière). From the retropharyngeal lymph nodes, the lymphatic drainage continues to the upper jugular nodes, the upper posterior triangle nodes and then further down to the lower neck in a step-wise fashion. The internal carotid artery is located postero-lateral to the fossa of Rosenmüller and is wrapped by the carotid sheath. The carotid sheath extends medially to form the prevertebral fascia. The retropharyngeal lymph node closely abuts the carotid sheath. An enlarged retropharyngeal lymph node caused by cancer metastasis may partially or completely encase the parapharyngeal internal carotid artery. Cancer can also spread along the carotid sheath superiorly into the foramen lacerum and into the intracranial cavity.

EPIDEMIOLOGY

In 2012, there were estimated to be more than 86 000 new cases of nasopharyngeal carcinoma (NPC) worldwide with over 50 000 deaths.[3] The incidence of NPC demonstrates one of the largest geographical variations among all head and neck cancers and the incidence in endemic areas can be 50 times higher than low prevalence areas.

The area with the highest incidence is in Southern China among the Cantonese population of the Guangdong Province. In Hong Kong, where the majority of the population is Guangdong in origin, the age-standardized incidence rate of NPC for men in Hong Kong was once 30 per 100 000 in the 1980s, but it has shown a gradual decline over the last 30 years.[4] Even inside China, there is a large variation in the incidence of NPC in different parts of the country. South China has the highest incidence, followed by Southwest China, Central China, East China, Northwest China and North China. The incidence in South China is three times higher than the second highest region, Southwest China.[5]

Outside China, Southeast Asia has the highest incidence of NPC, especially among countries with significant Malay and Indonesian populations. Populations in North Africa, especially Tunisia and Algeria, also have an elevated incidence.[6] Inuits in Alaska, North Canada and Greenland are another population group with elevated incidence of NPC.[7] Migrants to North America of South Chinese origin also have increased incidence though the incidence decreases among the second and third generation migrants.[8] The Japanese and Koreans, like Western populations, have an annual incidence rate of less than 1 case per 100 000.[7] The marked variation in the incidence of NPC implies that there exists a genetic susceptibility in the high incidence population.

The male to female ratio of the disease is 3 to 1, with a similar ratio observed in endemic areas and among low incidence populations. The peak age group of presentations of NPC in endemic areas is 50–55 years old, and it decreases with increasing age.

In Hong Kong, there has been a gradual decline in incidence of NPC in the last three decades. The incidence decreased by 30% from 38.5 per 100 000 males per year in 1980–84 to 20.2 per 100 000 males in 1995–99. The decreases in incidence in females followed a similar trend.[9] This decrease in not observed in other high-risk populations in Singapore, Malaysia or Guangdong province, People's Republic of China.[10]

AETIOLOGY

The exact sequence of events in the development of NPC has not been elucidated. A complex interplay of genetic susceptibility, Epstein—Barr virus (EBV) infection and environmental factors leads to the development of the cancer.[11]

Genetic factors

The presence of genetic susceptibility to NPC can be implied from the wide variation in cancer incidence across the world. Migrants from high-risk populations who settle in low incidence areas, like Southern Chinese emigrants to North America, have higher incidences than the native population though the incidence reduces in later generations.[8] On the other hand, migrants from low incidence areas do not experience an increased risk of NPC even when they emigrate to high incidence areas, like Indian emigrants in Singapore.[7] About 10% of NPC patients have familial clustering of cases.[12] Although a familial cluster can be explained by genetic factors, members of the same family, especially siblings, may be exposed to similar environmental factors. Therefore, the presence of familial clustering may imply the presence of either genetic or environmental factors, or both.

HLA subtypes and NPC

An early attempt to identify subgroups with genetic susceptibility was to correlate the risk of different human leukocyte antigen subtypes with the risk of developing NPC in high-risk populations in Singapore, Malaysia

and Hong Kong. Recent meta-analysis of the studies on HLA subtypes with NPC showed that HLA A2, B14 and B46 are associated with increased risk of NPC while HLA A11, B13 and B22 are associated with lower risk of NPC.

Recent genetic studies using advanced molecular biology techniques have yielded more information on the role of HLA genes in the development of NPC. A genome wide association study showed that genes at the 6p21 locus within the HLA region are strongly associated with NPC.[13, 14] Other genes in the HLA region were also associated with the development of NPC. The details of these genes are beyond the scope of this chapter. Hildesheim and Wang wrote an excellent review article on the genetic predisposition factors of NPC.[15] Current thinking is that individual HLA subtypes associated with NPC may have impaired immune response to EBV infection and clearance of the virus from the epithelium. The establishment of latent EBV infection in the epithelium of the nasopharynx may lead to pre-malignant changes in the epithelium, later progressing to invasive cancer.

Other cancer-associated genes including *MDM2* and *TP53* and the cell-migration gene *MMP2* have been shown in multiple studies to be associated with NPC, albeit in the later stages of cancer development.[16–20]

Environmental factors

Second and third generation Southern Chinese who had migrated to North America had a decreased risk of developing NPC compared with native Southern Chinese, though the risk was still higher than the local population. This implied that although genetic factors played a role in NPC development, environmental factors might also contribute to the cancer development.

Early studies in the 1970s and 1980s in Hong Kong identified that childhood consumption of salted fish increased the incidence of NPC in early adulthood.[21] Salted fish was shown to be carcinogenic when fed to rats in the laboratory.[22] Consumption of other preserved foods were also shown to increase the risk of development of NPC.[23] The carcinogenic effect of these preserved foods may be due to the high nitrosamine content.[24]

Multiple studies have shown that smoking increases the risk of NPC development and this risk increase is seen in both low and high incidence populations.[25, 26] However, the effect of smoking on NPC development is more pronounced on the well-differentiated type of NPC in the Western population than on the undifferentiated type of NPC in Southern China.[27] Jia and Qin have summarized the effect of environmental factors on the development of NPC in a systematic review.[28]

Epstein—Barr virus

Central to the pathogenesis of NPC is the carcinogenic Epstein—Barr virus (EBV). The virus was first associated with Burkitt lymphoma in sub-Saharan Africa. In the late 1960s, serological studies showed that NPC patients had elevated antibiodies against EBV, similar to levels found in patients suffering from Burkitt lymphoma.[29] Improvement in molecular genetics finally confirmed that EBV DNA sequences were found in the nucleus of the carcinoma cells of NPC.[30, 31] EBV is found only in the poorly differentiated and undifferentiated form of NPC, which is the prevalent histological subtype in high incidence areas.

The exact role of EBV in the development of NPC is still unknown. EBV typically infects B-lymphocytes and produces the acute syndrome of infectious mononucleosis. In the endemic areas, EBV has already infected the majority of the population by early adulthood, yet only a minority develop NPC. The virus does not commonly infect normal nasopharynx epithelium. It is postulated that the combination of genetic susceptibility, environmental factors and EBV infection all contribute to development of NPC. Genetic susceptibility may confer increased risk of a latent EBV infection, while environmental and dietary risk factors may transform the normal nasopharynx epithelium to a premalignant stage, supporting the EBV genome in the transformed nasopharynx epithelium. EBV genome, when incorporated into the nasopharyngeal epithelium, may cause malignant transformation. The virally infected cells may alter the cytokine environment and assist the cancer cells to avoid detection by host immune-surveillance. Tsao et al have summarized the current knowledge of EBV and NPC in a review article.[11]

The association of EBV with NPC can be exploited in the diagnostic process, therapeutic strategies and preventive treatment in NPC. These will be elaborated further later in the chapter.

PATHOLOGY

The commonest type of malignancy in the nasopharynx arises from the epithelium. The World Health Organization (WHO) originally categorized the epithelial malignancies from the nasopharynx into three subtypes: well-differentiated keratinizing squamous cell carcinoma (WHO type 1); non-keratinizing carcinoma (WHO type 2); and undifferentiated carcinoma (WHO type 3). The classification was later revised to two subtypes: keratinizing squamous cell carcinoma; and combining type 2 and type 3 into non-keratinizing carcinoma. The non-keratinizing carcinoma can be further subclassified as differentiated and undifferentiated types. The histology of the keratinizing squamous cell carcinoma is similar to other well-differentiated squamous cell carcinoma in the upper aerodigestive tract. On the other hand, there are some distinctive histological features in the non-keratinizing carcinoma, which is predominant in the high incidence/endemic regions. Histologically, the malignant cells are infiltrated with lymphocytes and plasma cells. These lymphocytes are predominately T-cell and are CD8+.[32] The term lymphoepithelial carcinoma has been coined to describe this histological feature that is different from other undifferentiated carcinoma of the head and neck region like sinonasal undifferentiated carcinomas. Other than the nasopharynx, lymphoepithelial carcinoma

can be found in salivary glands, paranasal sinuses and lungs. When lymphoepithelial carcinoma is found outside the nasopharynx, it is important to distinguish between primary cancer and metastatic cancer from the nasopharynx primary. **Figures 8.1** and **8.2** are histological slides showing a well differentiated NPC (WHO type I) and undifferentiated NPC (WHO type II) respectively.

EBV is ubiquitously found in all the cancer cells in non-keratinizing NPC. Immunostaining for EBV in the cancer cells can help to differentiate between NPC and different types of head and neck cancer, especially in tissue obtained from metastatic lymph nodes by excisional biopsy or fine needle aspiration. Immunostaining for EBV virus encoded small ribonucleic acid (RNA) (EBER) is commonly used to detect the presence of EBV inside the cancer cells.

In endemic areas like Southern China, non-keratinizing type of NPC constitute over 95% of the histological subtype of NPC. In low incidence populations like Japan or USA, non-keratinizing carcinomas still are the majority with only 25% of the NPC being the keratinizing subtype. Basaloid squamous cell carcinoma is a rare subtype of epithelial cancer seen at this site.

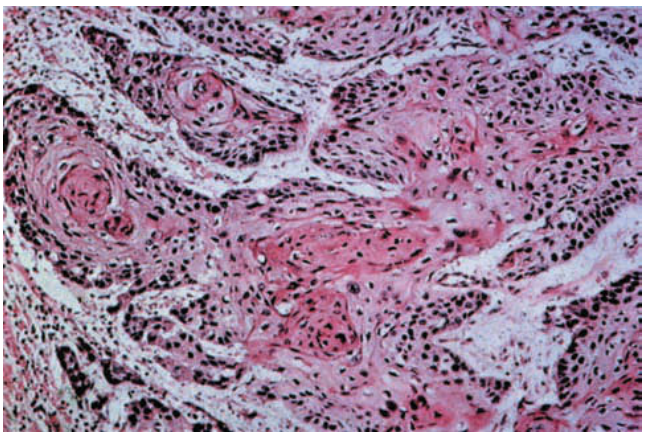

Figure 8.1 H&E stained histological slide of a keratinizing NPC (WHO type I). Note the keratinization.

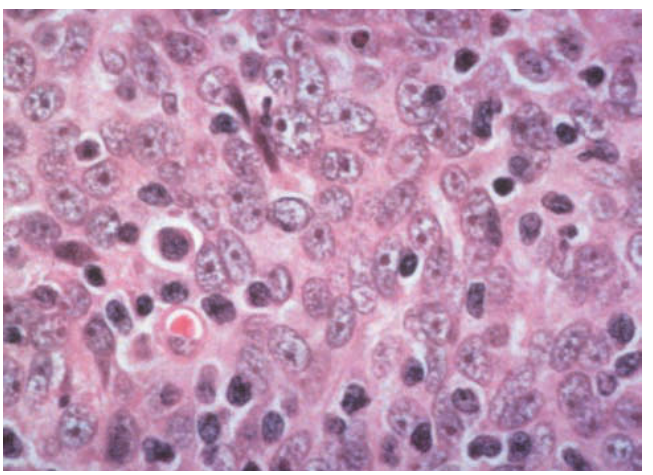

Figure 8.2 High power view of the H&E stained histological slide of an undifferentiated NPC (WHO type III). Note the abundant lymphocytes mixed with the cancer cells.

Salivary gland carcinomas are another important group of cancers that can occur in the nasopharynx, although the incidence is relatively low. The histology and behaviour of salivary gland carcinomas found in the nasopharynx are similar to other minor salivary gland cancers in the head and neck area.

Apart from epithelial carcinomas, soft tissue malignancies can occur in the nasopharynx, including sarcomas, lymphomas and malignant melanomas. Malignant fibrosarcomas and osteosarcomas are the commonest form of radiation-induced sarcomas in the nasopharynx in NPC patients treated with radiotherapy. For radiation-induced carcinomas, the histological subtype is typically well-differentiated squamous cell carcinoma with EBV absent in the cancer cells. Head and neck lymphoma frequently involves the lymphatic tissue in the Waldeyer's ring, including the lymphoid tissue in the nasopharynx. Certain lymphomas like Hodgkin lymphoma and T-NK lymphoma also harbour EBV in the cancer cells. It is important not to misdiagnose lymphoma as undifferentiated type of NPC based only on the presence of EBV in the biopsy. **Table 8.1** lists the types of benign and malignant neoplastic lesions that can occur in the nasopharynx.

TABLE 8.1 WHO classification of tumours of the nasopharynx

I Epithelial tumours	
a Benign	**b Malignant**
1 Papilloma	1 Nasopharyngeal carcinoma
2 Pleomorphic adenoma	2 Adenocarcinoma
3 Oncocytoma	3 Papillary adenocarcinoma
4 Basal cell adenoma	4 Mucoepidermoid carcinoma
5 Ectopic pituitary adenoma	5 Adenoid cystic carcinoma
	6 Polymorphous low-grade adenocarcinoma
II Soft tissue tumours	
a Benign	**b Malignant**
1 Angiofibroma	1 Fibrosarcoma
2 Haemangioma	2 Rhabdomyosarcoma
3 Haemangiopericytoma	3 Angiosarcoma
4 Neurilemmoma	4 Kaposi's sarcoma
5 Neurofibroma	5 Malignant haemangiopericytoma
6 Paraganglioma	6 Malignant nerve sheath tumour
	7 Synovial sarcoma
III Tumours of bone and cartilage	
IV Malignant lymphomas	
1 Non-Hodgkin lymphoma	
2 Extramedullary plasmacytoma	
3 Midline malignant reticulosis	
4 Histocytic lymphoma	
5 Hodgkin disease	

(*Continued*)

TABLE 8.1 (*Continued*) WHO classification of tumours of the nasopharynx

V Miscellaneous tumours	
a Benign	**b Malignant**
1 Meningioma	1 Malignant melanoma
2 Craniopharyngioma	2 Chordoma
3 Teratoma	3 Malignant germ cell tumours
VI Secondary tumours	
VII Unclassified tumours	
VIII Tumour-like lesions	
1 Cysts	
2 Meningocoele/meningoencephalocoele	
3 Granulomas	
4 Amyloid deposits	
5 Others	

Reproduced from Shao et al,[33] with permission.

CLINICAL FEATURES AND MODES OF PRESENTATION

Early cancers of the nasopharynx produce minimal and trivial symptoms that may be neglected by the patients and undetected by physicians. Moreover, the central location of the nasopharynx in the head means that cancer can spread in all directions, affecting many surrounding organs like the ears and eyes, producing symptoms that would not immediately relate to the nasopharynx. Broadly speaking, local symptoms and signs of NPC can be classified in to four categories: nasal; otological; cervical; and neurological. Patients rarely present with exclusive symptoms and signs of systemic metastasis without any local symptoms.

Nasal symptoms and signs

The majority of patients have some form of nasal symptom but may choose to neglect them until more sinister symptoms arise. Around 50% of the patients have suffered from nasal symptoms on presentation when asked directly. The most common symptoms are blood stained nasal discharge or post-nasal drip. If the tumour is large enough to obstruct the posterior choana, the patient may present with nasal blockage. Patients may also report cacosmia or a smell of blood due to bleeding from the tumour.

The nasopharynx is a difficult area to examine without special equipment. Physical examination often cannot identify the presence of the tumour unless the primary tumour has extended into the anterior nasal cavity or down into the oropharynx. Examination of the post-nasal space with a post-nasal mirror may reveal the presence of a tumour but this examination is difficult, especially in patients with strong gag reflex.

Otological symptoms and signs

Between 30% and 40% of NPC patients suffer from some form of ear symptom. Otological symptoms are usually caused by Eustachian tube dysfunction secondary to tumour bulk and/or invasion. Patients complain of recent onset of ipsilateral hearing loss, muffled sound, tinnitus and sensation of ear blockage. Unfortunately, patients and physicians may regard these as transient Eustachian tube dysfunction symptoms suffered during an upper respiratory tract infection, leading to a delay in diagnosis. Otoscopic examination will reveal the presence of a middle ear effusion. The nasopharynx should always be examined in adults with unexplained persistent middle ear effusion.

Neck symptoms and signs

An enlarging upper neck mass is the commonest symptom that prompts patients to seek specialist care. Up to 70% of patients with NPC have enlarged neck lymph nodes on presentation and one third of the patients have bilateral enlarged neck lymph nodes. The most frequently involved nodes are level II (upper jugular) and upper level V (apex of posterior triangle). Lymphatic spread of NPC occurs in an orderly fashion from superior to inferior,[34] with skip metastases being very rare. An isolated enlarged supraclavicular lymph node is almost never a lymph node metastasis from NPC. For patients with lymph node spread down to supraclavicular fossa, the disease is considered as a very advanced type of nodal metastasis, staged as N3b disease.

Occasionally, NPC patients can present with metastatic neck lymph nodes from an unknown primary. In these cases, the primary is usually very small and may not be obvious on endoscopy. New imaging modalities like magnetic resonance imaging and positron emission tomography (PET) may reveal the presence of small cancer in the nasopharynx. Additional investigations like serological testing for EBV and immunohistochemical staining of the cytological material for EBV can also point to a nasopharyngeal primary.

Neurological symptoms and signs

The presence of neurological symptoms usually signals advanced disease. Headache is the most common neurological symptom and is present in up to 20% of patients. The headache is usually localized to the vertex or occiput and caused by the invasion of the clivus bone by the tumour. Facial pain and midface numbness can also be a presenting symptom, caused by tumour invasion into the pterygopalatine fossa and the branches of V2. Cranial nerve (CN) palsies are caused by extension of the tumour into the skull base or intracranially. Common cranial nerves to be involved at presentation are V2, V3 and VI. Involvement of CNIII and CNIV are indicative of cavernous sinus invasion by tumour. Rarely, patients present with ophthalmoplegia, decreased vision and proptosis caused by direct invasion of the tumour into the orbital apex. Trismus is rare unless the tumour has directly invaded the pterygoid

muscles in the masticator space. Horner syndrome can occur if the tumour or metastatic lymph node encases the carotid vessels. This is an uncommon mode of presentation as the carotid sheath is a tough fascia that impedes direct tumour invasion. The presence of Horner syndrome is usually associated with other cranial nerve involvement like CNX and CNXI. Patients from endemic regions with isolated CN palsies should be investigated for the presence of NPC, either by imaging or by nasal endoscopy.

Symptoms of systemic metastasis

NPC presentation with systemic metastasis is uncommon and is usually associated with advanced local or nodal diseases. Common sites of distant metastases are liver, lung and bone, with brain metastasis being rare.

One special scenario that can lead to confusion is the finding of histologically proven lymphoepithelial carcinoma in a lung nodule, which can be a primary lymphoepithelial carcinoma of the lung or distant metastasis from a nasopharyngeal primary. A PET scan can help differentiate between a lung primary and a distant metastasis. If the disease is confined to the lung on imaging, the patient should be treated as appropriate for a primary lung cancer.

Para-neoplastic syndrome

Around 1% of NPC patients develop dermatomyositis as a para-neoplastic syndrome. A study performed in an NPC endemic area showed that up to 12% of dermatomyositis patients developed NPC.[35] Dermatomyositis can develop concurrently with NPC, late after the diagnosis of NPC or months before the NPC is clinically and symptomatically apparent.

DIAGNOSIS

An approach to diagnosis based on the resources and expertise available should be formulated and followed to shorten the time taken for diagnosis. Such a guide to the diagnostic process is especially useful in areas where NPC is endemic. **Figure 8.3** outlines an approach to the diagnosis of NPC in an endemic region.[36] A good history, together with a thorough clinical examination including endoscopy of the nasopharynx, is the basis for making the diagnosis. In most patients, a tumour mass will be found in the nasopharynx and a biopsy should be taken without delay. In less than 5% of patients, the nasopharynx may appear normal and other investigations may then be necessary to confirm or definitively exclude the diagnosis of NPC.

History

NPC should be a differential diagnosis for patient who presents with any of the four groups of symptoms discussed above, especially if they are from a high incidence region. Symptoms of tinnitus, ear blockage or blood stained nasal discharge may seem benign but they should be investigated further if no apparent cause is found. The ancestry of the patient should be inquired about, especially in Chinese patients, who should be asked whether they are from Northern or Southern China. A family history of NPC is also important as 10% of NPC patients have familial clustering of the cancer.

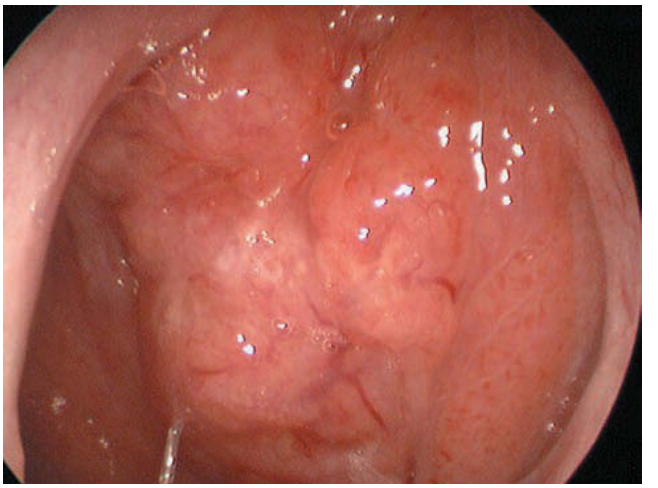

Figure 8.3 View of the nasopharynx through a 0° rigid nasoendoscope. A tumour can be seen obliterating the left fossa of Rosenmüller extending to the right across the midline.

General examination

A full head and neck examination is essential in all patients. Care should be taken to look for otitis media with effusion (OME), CN lesions and cervical lymphadenopathy. When nodes are palpable, their site and size must be carefully assessed as part of the staging process.

Examination of the nasopharynx and nasopharyngoscopy

Traditionally, examination of the nasopharynx was performed by the indirect mirror examination. This technique of examining the nasopharynx is often inadequate due to poor illumination and a strong gag reflex. Additionally, biopsy of any lesion found in indirect mirror examination is nearly impossible in the outpatient setting. Substituting the post-nasal mirror with a 70 degree or 90 degree telescope may solve the problems of poor illumination and poor visualization but the problems of gag reflex and inability to obtain biopsy would still be present.

Antegrade nasopharyngoscopy can be performed with either a rigid telescope or a flexible endoscope. With improvements in technology, the diameter of the new endoscopes is smaller, with improved optics. Both rigid and flexible endoscopes are now available with diameters of less than 4 mm. The choice of using a flexible or rigid endoscope depends on the clinical setting. A flexible endoscope would be more desirable if the larynx and hypopharynx need to be examined in the same setting or if nasal anatomy precludes the use of a rigid telescope. For rigid telescopes, a 0 degree telescope provides a more

direct view but a 30 degree telescope can be turned to examine the lateral wall of the nasopharynx and fossa of Rosenmüller better. **Figure 8.3** shows the view of the nasopharynx with a tumour left fossa of Rosenmüller extending to the left nasopharynx.

Ideally, the nasal cavities should be prepared by the application of local anaesthesia and vasoconstrictor prior to performing nasopharyngoscopy. Traditionally, 5% cocaine was used given its anaesthetic and vasoconstriction properties. However, owing to the disadvantages of being a controlled drug with significant cardiovascular toxicities, other agents are preferred: 2–5% lignocaine with the addition of a vasoconstrictor like 1 : 10 000 adrenaline, 0.5% phenylephrine or 0.1% xylometazoline. The local anaesthetic can be applied by placing cotton pledges soaked with the drug or by spraying the drug into the nasal cavities. The endoscopy should be performed a few minutes later to allow the vasoconstrictors to act so that the nasal mucosa can shrink adequately for better inspection of the nasal cavities and nasopharynx. Occasionally, in patients with deep fossa of Rosenmüller or bulky Eustachian tube cushions, the fossa cannot be adequately visualized. The patient should then be instructed to swallow and then say 'arh'. This will close the velopharynx and pull the Eustachian cushions anteriorly, exposing the deep fossa.

Most of the cancers are readily apparent under endoscopy, presenting as a mass with abnormal capillaries on the surface with areas of ulceration. Occasionally, the tumours are infiltrative and no mass may be seen. However, close inspection will reveal abnormal capillaries in the mucosa; easy contact bleeding is a sign of NPC.[37] Cross-sectional imaging, especially MRI, will pick up this type of submucosal NPC.

Biopsy of the nasopharynx

If an obvious tumour can be seen during endoscopy in the outpatient setting, biopsy of the lesion can usually be performed concurrently. Flexible endoscopes with a biopsy channel for use in nasopharyngoscopy usually have a small biopsy channel; thus, it is advisable to obtain multiple biopsies to avoid inadequate tissue for histological diagnosis. Alternatively, a biting ethmoid forceps used in endoscopic sinus surgery can be passed into the nasal cavity above or below the endoscope under endoscopic guidance for obtaining biopsy (**Figure 8.4**). For procedures using rigid endoscopes, the biopsy technique is similar. Some mild mucosal bleeding can be expected after the biopsy but this should be self-limiting. Patients on anticoagulation drugs should have the coagulopathy corrected before the biopsy procedure.

Biopsy under general anaesthesia may be required if multiple deep biopsies are needed to rule in or rule out the diagnosis of NPC. Patients with metastatic neck lymph nodes with an unknown primary, persistently raised tumour markers and normal nasopharynx on endoscopy or inconclusive biopsy results will be candidates for general anaesthesia. Multiple deep biopsies including biopsies from the roof of nasopharynx, central nasopharynx and mucosa of both fossae of Rosenmüller should be obtained.

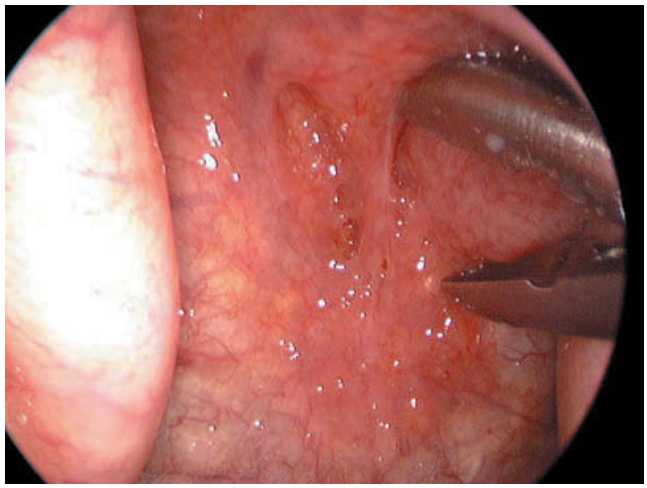

Figure 8.4 Biopsy of the left nasopharynx under direct visualization from a 0° nasoendoscopy. The nasoendoscope was introduced through the right nostril while the ethimoid biting forceps was introduced through the left nostril. Alternatively, both instruments can be introduced through same nostril after decongesting the nasal cavities.

DIFFERENTIAL DIAGNOSIS

Several entities may resemble NPC on clinical examination. These include inflammatory disease in the nasal cavities like rhinosinusitis or nasal polyposis, infections in the nasopharynx including viral infections or tuberculosis of the nasopharynx and other rare malignancies, such as T-NK lymphoma (midline lethal granuloma), mucosal melanoma, sinonasal undifferentiated carcinoma and olfactory neuroblastoma involving the nasopharynx.

LABORATORY TESTS

Although biopsy of the nasopharynx remains the gold standard in diagnosis of NPC, several laboratory tests can aid the diagnosis or be useful for monitoring and screening the disease. Blood tests are especially useful for screening purposes as they are less invasive and easier to deploy than endoscopic examination of the nasopharynx.

EBV antibodies serology

The first association of endemic NPC with EBV was found when patients with NPC regularly were found to have elevated levels of EBV antibodies in the serum.[38] IgA antibodies against viral capsid antigen (VCA), early antigen (EA) and EBV nuclear antigen 1 (EBNA1) are commonly used as tumour markers to screen for NPC. On the other hand, serum EBV IgG titre signifies prior infection by the virus and elevated serum EBV IgM titre indicates recent infection. EBV IgG serology and IgM serology are not useful in screening NPC as most adults will have been infected by EBV at an earlier age. EBV IgA VCA is sensitive but not specific for NPC while EBV IgA EA is specific but not sensitive for detecting NPC. Combining both tests

can increase the sensitivity and specificity of the serological tests. A large single centre review of more than 5000 subjects, of which 215 suffered from NPC, showed the sensitivity and specificity of EBV IgA VCA to be 89% and 80% while the sensitivity and specificity of EBV IgA EA was 63% and 95%.[39] A recent meta-analysis of 20 published reports on EBV IgA VCA serology sensitivities in Chinese literature showed a similar sensitivity of around 91%.[40]

EBV serology is not an ideal tumour marker for NPC as the serology has weak correlation with the stage of the disease, unable to reflect the tumour response to therapy and does not show increasing titre in recurrent disease.[41] Despite its deficiency, EBV serology is still widely employed in endemic areas for screening or initial diagnostic work up, due to its low cost.

Plasma EBV DNA titre

EBV genome is found in all cancers cells of the endemic form of NPC and EBV DNA will be shed into the patients' blood stream during cell turnover. More advanced stage NPC will have a higher tumour load and larger cancer cell turnover. Detection of EBV DNA in the plasma could therefore be used as a tumour marker of NPC. Improvements in molecular genetics studies has allowed the number of copies of the DNA in the plasma to be assessed using the quantitative (real-time) polymerase chain reaction (rt-PCR). Establishing a threshold level of plasma EBV DNA can help to differentiate between a genuine case of NPC and low levels of DNA due to reactivation of infection. Lo et al first reported the use of qt-PCR assay of EBV DNA in plasma for the detection of NPC.[42,43] The reported sensitivity and specificity of plasma EBV DNA for NPC detection were 96% and 93% respectively. Studies comparing EBV serology with plasma EBV DNA for detection of NPC have found the latter to be a superior test.[33,41]

Apart from diagnostic and screening purposes, plasma EBV DNA levels can have a prognostic implication.[44,45] A high level of EBV DNA before treatment correlates with the larger tumour load and more advanced stage of the cancer.[46] Plasma EBV DNA levels rapidly decrease to undetectable or very low levels within 1–2 weeks after completion of treatment.[47] Persistently elevated plasma EBV DNA titre after treatment may signify persistent loco-regional disease or development of distant metastasis and has been used as a justification for adjuvant chemotherapy.[48,49] An initial drop of plasma EBV DNA levels after treatment and a later progressive rise in the level may represent tumour recurrence.[49] Plasma EBV DNA titre has also been used for monitoring of treatment response during chemotherapy in lieu of imaging, reducing the cost and inconvenience to the patients.[50] Overall, plasma EBV DNA assessment has proved to be a versatile tumour marker for NPC.

The only caveat when interpreting plasma EBV DNA is that levels will be elevated in any disease associated with EBV, like infectious mononucleosis and EBV-associated lymphoid malignancy.[51] Also, plasma EBV DNA levels lack sensitivity in detecting small local recurrences after radiotherapy.[52]

Nasopharyngeal brushing for EBV DNA

To tackle the problem of elevated plasma EBV DNA in other EBV-associated diseases, direct detection of EBV in the nasopharynx has been devised.[53,54] Brushing of the nasopharynx is performed and the cells obtained are sent for EBV DNA detection with qt-PCR. Theoretically, this test should be more sensitive and specific than plasma EBV DNA level. Although early brush designs fell out of favour due to being impracticable, newer designs of transoral brushing and detection of EBV DNA show promising results. The test is easy to perform and has a very high sensitivity and specificity of 98.9% and 99.3% respectively.

Cytology

When analyzed by an experience cytologist, cytological smears from the fine-needle aspiration of enlarged neck lymph nodes can often differentiate between metastasis from squamous cell carcinoma and undifferentiated carcinoma. With the addition of immunohistochemical staining for EBV RNA (EBER), a definitive diagnosis of NPC with neck lymph node metastasis can be made. Performing fine-needle aspiration avoids open biopsy of the neck lymph node.

IMAGING

Imaging studies are indispensable for staging of the disease and can also aid in the differential diagnosis in cases with atypical presentations. When cost is not a concern, imaging studies are useful for post-treatment monitoring.

Plain radiograph

A plain radiograph of the nasopharynx is neither sensitive nor specific enough for any clinical use and has been superseded by other modalities.[55] A plain chest X-ray can be done as an initial screening for lung metastasis and general health status. Orthopantomogram is often performed by a dentist treating patients prior to radiotherapy.

Computerized tomography

The use of a computerized tomography (CT) scan as a staging modality has been replaced by magnetic resonance imaging (MRI) as more and more centres adopt newer three-dimensional radiotherapy techniques. CT scans are still used by many clinicians as they are more widely available and can clearly show bone erosions in the skull base. Newer scanners can reconstruct the images in any plane with fine details and high accuracy. The new linear accelerators capable of three-dimensional radiotherapy treatments have inbuilt CT scanners, an essential tool for radiation planning.

Magnetic resonance imaging

MRI is the preferred imaging modality for NPC staging and treatment because of its superior soft tissue resolution. For assessment of tumour extent, MRI can better delineate parapharyngeal extension of tumour, perineural spread and marrow infiltration. MRI can also differentiate between tumour infiltration from retained secretions in the paranasal sinuses, and can define better the limits of the optic chiasma, optic nerves and brainstem. Accurate delineation of these structures is important for preservation of these organs at risk in the newer radiotherapy techniques. New generations of radiation planning software systems allow fusion of MRI with CT images for determination of tumour extent and radiation planning, allowing the best of both worlds. Additional imaging modalities like PET-CT can also be fused.

MRI is more useful than CT in monitoring the disease after treatment and imaging recurrent diseases. Post-treatment fibrosis can be difficult to differentiate from recurrent tumour. Traditional MRI sequences may not be much superior to CT[56] but with newer MRI sequences like diffusion weighted images, the diagnostic accuracy of MRI for recurrent disease has increased.[57] The diagnostic accuracy of modern MRI is on par with PET-CT in detecting residual and recurrent disease.[58]

Ultrasound scan

Ultrasound scan is a widely available, inexpensive and non-invasive tool especially suited for investigating neck lymph node metastasis. Ultrasound combined with fine-needle aspiration cytology can achieve a very high sensitivity and specificity for detection nodal metastasis in NPC. In patients with equivocal findings of nodal status on cross-sectional imaging, additional ultrasound guided fine-needle aspiration cytology can provide the diagnosis without resorting to expensive functional imaging modalities like PET-CT scan. The disadvantage of ultrasound scanning is that its accuracy is dependent on the operator. Also, the images and information acquired cannot be fused with other cross-sectional images.

Positron emission tomography

PET is increasingly being used in the management of NPC. A PET scan is a functional imaging study and is normally combined with a cross-sectional imaging modality like a CT scan for anatomical localization. For use in NPC, 18F fluoro-deoxyglucose (18FDG) is the most frequently used isotope. 18FDG is similar to glucose and areas with increased glucose metabolism will be highlighted on PET scans. PET-CT can supplement other imaging modalities in detecting the tumour extent and nodal metastasis but cannot replace MRI scans. PET-CT is less accurate in the delineation of tumour extent in the skull base.[59] Since PET-CT is a whole body scan, it can also detect distant metastases in addition to loco-regional disease extent. Patients with bulky nodal disease have an increased chance of distant metastases, and PET-CT is highly recommended for this group of patients prior to treatment.

PET-CT is very useful in assessing residual and recurrent disease after treatment. Conventional MRI is inferior to PET-CT and the clinician may need serial MRI scans to detect recurrence.[60] PET-CT detects both loco-regional failures and distant failures and is especially recommended in patients with a rising trend of EBV DNA titre after treatment.[61]

STAGING

The biological behaviour and prognosis of NPC is vastly different from squamous cell carcinoma of the head and neck region and the staging system is also different. The modified Ho's stage classification was widely used in the last millennium and was based on the treatment results with conventional two-dimensional radiotherapy techniques. This has now been replaced by the newer International Union Against Cancer (UICC)/American Joint Committee on Cancer (AJCC) staging systems that rely more on cross-sectional imaging for staging and reflect the improved outcomes with newer radiation techniques like intensity modulated radiotherapy and concurrent chemoradiotherapy. The new AJCC eighth edition staging of NPC has several major changes reflecting these improvements.[62] **Table 8.2** sets out the TNM and group stages as per the eighth edition of the AJCC system.

PRIMARY TREATMENT

The non-keratinizating subtype of NPC is a very radiosensitive tumour. Radiotherapy is the mainstay of treatment for primary NPC and surgical treatment is reserved for salvage of radiation failures. The two major advances in NPC management are the introduction of intensity-modulated radiotherapy (IMRT) and the discovery that concurrent chemoradiation improves the efficacy of radiotherapy.

Radiotherapy

Radiotherapy is the cornerstone of loco-regional treatment for all stages of NPC without distant metastases (i.e. from stage I to IVB diseases). Early stage diseases, including stage I and low-risk stage II NPC, can be treated with radical radiotherapy alone. Stage II disease with higher tumour load and stage III, IV disease require combination chemotherapy and radiotherapy.

Intensity-modulated radiotherapy (IMRT) is the standard of care for radiation treatment of NPC. Radiotherapy planning starts with making an individualized immobilization device, usually a thermoplastic cast for the head and neck for each patient. Then, a planning CT scan is obtained with the patient in cast and in treatment position.

TABLE 8.2 AJCC stage classification for NPC[62]*

Primary tumour (T)>		Regional lymph nodes (N)	
Tx	Primary tumour cannot be assessed	**N1**	Unilateral metastasis, in cervical lymph node(s), and/or unilateral or bilateral metastasis in retropharyngeal lymph nodes, 6 cm or less, above the caudal border of cricoid carilage
T1	Tumour confined to nasopharynx, or extends to oropharynx and/or nasal cavity without parapharyngeal space involvement	**N2**	Bilateral metastasis in cervical lymph node(s), 6 cm or less above the caudal border of cricoid cartilage
T2	Tumour with extension to parapharyngeal space and/or infiltration of the medial pterygoid, lateral pterygoid, and/or prevertebral muscles	**N2**	Metastasis in cervical lymph node(s) greater than 6 cm in dimension and/or extension below the caudal border of cricoid cartilage
T3	Tumour invades bony structures of skull base cervical vertebra, pterygoid structures, and/or paranasal sinuses		
T4	Tumour with intracranial extension and/or involvement of cranial nerves, hypopharynx, orbit, parotid gland and/or infiltration beyond the lateral surface of the lateral pterygoid muscle		

Metastatic disease (M)	
M0	No distant metastasis
M1	Distant metastasis present

Stage groups			
I	T1	N0	M0
II	T1 T2	N1 N0, N1	M0 M0
III	T1, T2 T3	N2 N0-, N1, N2	M0 M0
IVA	T4 Any T	N0, N1, N2 N3	M0 M0
IVB	Any T	N3	M0
IV	Compressed previous stage IVB now IVA		

* reprinted with permission[62]

The planning CT scan is used for localization of targets and normal tissues. The required doses to targets and the dose constraints to normal tissues are input into the computer planning system, which will generate the optimal radiation plan that concentrates the radiation dose in targets while minimizing the dose to normal tissues.

There are different treatment targets: gross tumour volume (GTV, both for the primary in NP and for involved neck nodes); clinical target volume (CTV, which includes the GTV and covers for subclinical disease spread around NP and neck); planning target volume (PTV, which includes the CTV with a margin to allow for possible errors in daily positioning and treatment of patient during radiotherapy).

GTVs will include the tumour in NP and any enlarged (>6 mm) retropharyngeal and neck nodes or lymph nodes with necrotic centres. CTV1 includes the GTVs with margin and requires radiation dose of around 70 Gy. The high risk subclinical disease is covered by CTV2, which include CTV1 with margin plus areas at risk of microscopic involvement, including the entire NP, retropharyngeal nodal regions, skull base, clivus, pterygoid fossae, parapharyngeal space, sphenoid sinus, and the posterior part of the nasal cavity/maxillary sinuses that includes the pterygopalatine fossae.[63, 64] CTV 2 requires at least 60 Gy for treatment. The neck is always irradiated together with the primary and the CTV would include bilateral level I through V nodal regions. At levels with nodal involvement, the dose to CTV should be at least 60 Gy. A lower dose, 54–60 Gy, may be given for prophylactic irradiation of uninvolved nodal regions.

IMRT has 'dose-painting' capacity that allows different dose levels to different regions to be applied in the same treatment. For example, in a course of IMRT with 33 fractions over 6.5 weeks, CTV1 may be treated to 70 Gy at 2.12 Gy/fraction while CTV2 can be treated to 66 Gy at 1.82 Gy/fraction. This simultaneous-integrated boost technique allows for a degree of accelerated fractionation in tumour without overdosing the normal tissues. With IMRT, local control rates of over 90% have been reported. The complications from conventional two-dimensional radiotherapy such as hearing loss, xerostomia, temporal lobe neuropathy, trismus and neck fibrosis, are reduced.[65] **Figure 8.5** shows a screen capture from the planning software depicting the dose-painting technique of IMRT.

Chemotherapy

NPC is known to be sensitive to both chemotherapy and radiotherapy. Several studies combining chemotherapy and radiotherapy in treatment of NPC have been published, but the sequence of administration of chemotherapy in relation to radiotherapy and the choice of chemotherapy is important.

The pivotal Intergroup study 0099 established concurrent cisplatin during radiotherapy followed by adjuvant cisplatin and fluorouracil as the standard of care for advanced NPC.[66] The Meta-Analysis of Chemotherapy in Nasopharyngeal Carcinoma (MAC-NPC) showed a survival benefit with the use of chemotherapy in addition to radiotherapy in treatment of NPC.[67] The effect was most significant when chemotherapy was used concurrently with radiotherapy (pooled hazard ratio of death: 0.6). An update of the meta-analysis was reported in 2014

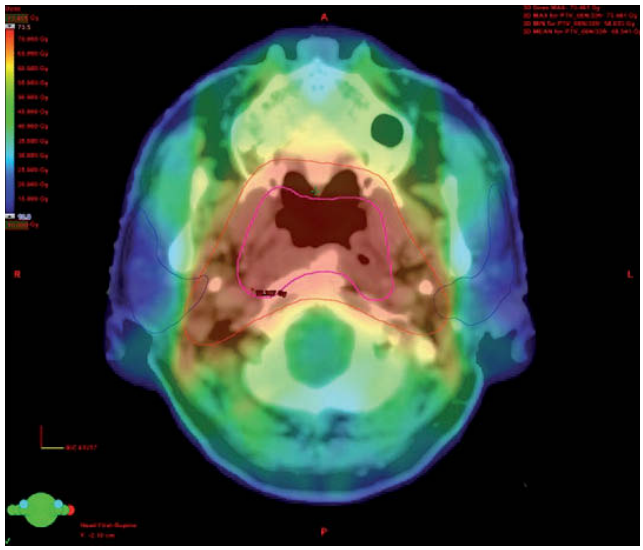

Figure 8.5 Dosimetry plot of IMRT on the nasopharynx. The patient was treated with dose-painting with IMRT: the NP was treated to 70 Gy while the high-risk area was treated to 66 Gy in 33 fractions. The parotids on both sides were treated to 20 Gy or less. Red ~ 65–70 Gy, green ~ 45–50 Gy and blue ~ 20 Gy.

that included additional trials (overall 19 trials and 4798 patients) since the last meta-analysis.[68] There was a significant benefit of chemotherapy in addition to radiotherapy in improving overall survival (hazard ratio: 0.79). There was a significant interaction between treatment effect on overall survival and the timing of chemotherapy, in favour of concurrent chemotherapy with or without adjuvant chemotherapy compared with induction or adjuvant chemotherapy alone.

Cisplatin is the usual agent used concurrently with radiotherapy. Weekly (30–40 mg/m^2) or 3-weekly (100 mg/m^2) cisplatin are acceptable standards of care. A total dose of 200 mg/m^2 administered during radiotherapy is required to benefit survival. The benefit of adjuvant chemotherapy in addition to the concurrent chemoradiotherapy is less certain. Recently, there has been renewed interest in the use of induction chemotherapy, especially in addition to concurrent chemotherapy. The preliminary results of the NPC-0501 study reported from Hong Kong showed that outcomes were not significantly impacted by changing from the concurrent-adjuvant sequence to induction-concurrent sequence with potential benefit of using induction cisplatin and capecitabine in place of cisplatin and fluorouracil.[69]

Unlike squamous cell carcinoma of the head and neck region, epidermal growth factor receptor tyrosine kinase inhibitors like cetuximab had not been shown to be beneficial, either as a single agent for palliative treatment or in addition to chemoradiation for primary treatment. As of 2014, there are no randomized controlled trials on the benefits of adding cetuximab in the treatment of NPC. There are small-scale phase II open labelled trials on the addition of cetuximab with concurrent chemoradiation for treatment of primary NPC[70] or cetuximab with carboplatin for recurrent/metastatic NPC that failed first line chemotherapy.[71] The results showed acceptable toxicities but no definite superiority. Further research is required to develop suitable target therapy for NPC.

With the advancement of radiotherapy and improved local control, distant metastases become the dominant pattern of disease failure. Patients who recur now have usually been exposed to cisplatin and fluorouracil in primary treatment. New chemotherapy agents such as taxanes and gemcitabine have been found to be useful in the treatment of recurrent or metastatic NPC. How best to incorporate these newer agents into the primary treatment of NPC and how to use newer prognostic markers like EBV DNA in selecting high-risk patients for more aggressive treatment are areas of intense research.

MONITORING OF TREATMENT AND FOLLOW-UP PLAN

With the introduction of concurrent chemoradiotherapy, persistence of local and regional disease has dropped to less than 10%. Still, it is prudent to confirm that the disease has fully regressed after treatment. Patients should have endoscopy and biopsy of the nasopharynx to confirm disease resolution after the completion of radiotherapy. This should not be performed too early after radiotherapy as tumour cells continue to undergo apoptosis weeks after completion of radiotherapy. One observational study has shown that patients with a nasopharyngeal biopsy showing tumour cells at 8 weeks after radiotherapy will continue to undergo complete regression by 12 weeks, suggesting that disease should only be considered persistent if biopsy is positive at 12 weeks after radiotherapy.[72]

Long-term follow-up of all patients is essential. Most failures occurs within 2 years of treatment[73] but a small percentage of patients develop local recurrence more than 10 years after the primary treatment.[74] Distant failure can occur several years after treatment and long-term complications of radiotherapy may not be seen until 5 years after treatment. There is no consensus on the optimal follow up schedule. Given the insight from patterns of failure, regular 2–3-monthly follow-up in the first 2 years, increased to 3–4 times per year in the third to fifth years, followed by 6-monthly or yearly reviews is advisable.

SALVAGE TREATMENT

Salvage treatment for NPC is moderately successful but with significant morbidities. A large survey of 200 local failures treated with different modalities showed an overall 3-year survival of 74%.[75] As patients with recurrences have already been exposed to the toxicities of previous treatment, the choice of the salvage treatment would need to consider the tolerance of the normal tissue.

Radiotherapy for local failures

Radiotherapy for treatment of local failures can be delivered by external beam or by local brachytherapy. The main limiting factor in re-irradiation is the tolerance of the vital organs like brainstem, optic chiasma and temporal lobe to radiation. Traditional two-dimensional re-irradiation for local failure had poor results, with one study showing a 5-year survival of only 7.6%.[76] The dismal result was due to the dosimetry constraints to avoid excessive radiation to vital organs. With the development of three-dimensional radiotherapy techniques like 3D stereotactic radiotherapy and IMRT, it is possible to reduce the dose or radiation to these vital organs;[77–79] however, adjacent non-vital organs will still be exposed to higher doses. A small series of 30 patients showed the 5-year overall survival and local control using stereotactic radiotherapy to salvage local recurrence were 40% and 57% respectively.[80]

Brachytherapy delivers a high dose of radiation with limited penetration inside the nasopharynx to treat local failures without deep invasion. The main radioactive sources used are iridium-192 (Ir192) and gold 198 (Au198). Both isotopes emit gamma radiation. Delivering brachytherapy needs special techniques. For Ir192, the radioactive source is loaded into a tailor-made plastic mould fitted into the nasopharynx of the patient beforehand. The plastic mould is placed into the nasopharynx via the oral cavity under local anaesthesia.[81, 82] For Au198, the gold grains are implanted to the nasopharynx after the soft palate is split open under general anaesthesia.[83] Both techniques are only suitable for small tumours less than 2 cm in maximal dimension. The 5-year survival rates for salvaging with this technique is in the range of 50–60%.[84]

Radiotherapy for nodal failures

In the era of concurrent chemoradiation, isolated nodal failure is an uncommon event. Only 5% of patients may suffer from isolated nodal failures.[73] Therefore, it is imperative to investigate for any simultaneous local recurrences in patients who present with nodal recurrence. Patients who have persistently enlarged neck lymph nodes 3 months after completion of radiotherapy should be considered to have persistent nodal diseases and offered salvage treatment.[85] In the era of 2D radiation, re-irradiation of isolated nodal failures showed poor results, with less than 20% 5-year survival.[86] Additional radiotherapy also increases the radiation damage to the soft tissues in the neck; therefore, re-irradiation treatment for salvaging nodal failure is not recommended.

Due to the limited penetration of brachytherapy techniques, they can be used for treatment of nodal failure in conjunction with surgical resection of the nodal metastasis. This will be discussed later in the chapter.

Surgery for local failure

The nasopharynx is notoriously difficult to access surgically. Most routes of access require facial incisions and multiple osteotomies, and transgress a significant amount of normal tissue to expose the nasopharynx. Therefore, surgical resection of the nasopharynx, namely nasopharyngectomy, is only reserved for salvaging radiation failures. The decision to offer nasopharyngectomy for salvaging local failures depends on the location of the tumour and the general condition of the patient. The patient should be fit for a 5-hour operation under general anaesthesia. Tumours that show internal carotid artery encasement, extensive skull base infiltration or intracranial extension are not suitable for salvage surgery. Alternative salvage treatment should be offered instead. Since the introduction of nasopharyngectomy for salvaging NPC local failures in the 1980s, significant experience has accumulated at several large volume centres. Nasopharyngectomy in experienced hands has low peri-operative mortality and acceptable morbidities. The 5-year local control is in the range of 70%. A large case series in treatment of local failures showed that there was no significant difference in terms of overall survival in patients treated with a second course of radiotherapy or surgery but nasopharyngectomy was associated with lower morbidities. Only patients with rT1 and rT2 diseases had survival advantage; patients with rT3 and rT4 diseases showed no improvement in survival with retreatment by either means.[75]

As the nasopharynx is in the central part of the head, various approaches can be used. Below is a brief discussion of various approaches.

TRANSPALATAL APPROACH – INFERIOR APPROACH

This approach is extensively used for salvaging NPC local failures. A mucoperiosteal flap of the hard palate is elevated from the bony hard palate from anterior to posterior to expose the attachment of the soft palate. The soft palate is then detached from the bony hard palate and retracted inferiorly to expose the nasopharynx. The posterior edge of the hard palate can be removed to increase the exposure and the recurrent tumour excised under direct vision. The palatal flap is subsequently re-sutured back to the anterior hard palate mucosa at the conclusion of the procedure. The advantages of the procedure are minimal bone removal and no facial incision; disadvantages include limited lateral access to the parapharyngeal space and risk of palatal fistula. Fee et al reported a series of 37 patients treated with this approach with a 5-year overall survival of 52% and local control of 67%.[87]

TRANSCERVICO-MANDIBULO-PALATAL APPROACH – INFEROLATERAL APPROACH

Morton et al first described this approach for salvaging NPC in 1996.[88] This approach improves the exposure of a transpalatal approach by the addition of the lip-splitting mandibulotomy. The mandible is swung laterally and the floor of mouth incision is extended superiorly along the anterior pillar of the tonsil to divide the soft palate from the hard palate. The nasopharynx can then be visualized from the inferio-lateral fashion. This gives a wider view and can offer access to the ipsilateral parapharyngeal space.

However, owing to disruption of large amounts of normal anatomy, significant long-term morbidities are associated with this technique. King et al reported the morbidity profile in a series of 11 patients who underwent nasopharyngectomy via this approach: eight patients had a palatal defect; six patients suffered from trismus; six patients had dysphagia; and three patients had malunion of the mandible.[89]

MIDFACIAL DEGLOVING APPROACH – ANTERIOR APPROACH

The procedure is similar to the midfacial degloving approach for resection nasal cavity cancers and juvenile nasopharyngeal angiofibromas. To increase the exposure of the nasopharynx and room for instrument manipulation, bilateral medial maxillectomies and posterior nasal septectomy should be performed. In a series of 15 cases, the surgeon was able to achieve clear margins in 12 cases but the long-term oncological outcome was not reported.[90] The obvious advantages of this approach are the lack of facial scar and avoiding the risk of a palatal fistula. Exposure can be poor, even when the medial maxillary walls are removed. There is also limited lateral access with this approach. In one cohort, the oncological outcome of the midfacial degloving approach was significantly worse than the maxillary swing approach.[91] The postulation was that NPC frequently had lateral extension and inability to remove disease in the lateral nasopharynx and parapharyngeal space might contribute to the poor oncological outcome.

MAXILLARY SWING APPROACH – ANTERO-LATERAL APPROACH

The approach starts with a standard incision for radial maxillectomy – the Weber-Ferguson-Longmire incision. Osteotomies are made: at the anterior maxilla inferior to the orbital rim; midline at the hard plate just lateral to the nasal septum; at the anterior zygoma separating the maxilla from the zygoma; and finally between the posterior maxillary wall and the pterygoid plates at the maxillary tuberosity. The maxilla is left attached to the anterior cheek skin and the whole maxilla with the cheek skin is retracted laterally to expose the parapharyngeal space and nasopharynx.[92] This approach provides wide exposure of the nasopharynx and parapharyngeal space, allowing the surgeon to perform resection of the tumour not only in the nasopharynx centrally but laterally in the parapharyngeal space and to the origin of the pterygoid muscles. In addition, the surgeon can localize the parapharyngeal internal carotid artery by palpation during dissection in the parapharyngeal space. After performing the resection, the maxilla is put back and the bony osteotomies fixed with titanium plates. Wei reported his 20 years experience of the maxillary swing approach in 246 patients. The treatment results were very encouraging with a 5-year local control of 74% and 5-year disease-free survival of 56%.[93] The disadvantage of this approach is the presence of a facial scar, risk of trismus and palatal fistula formation.

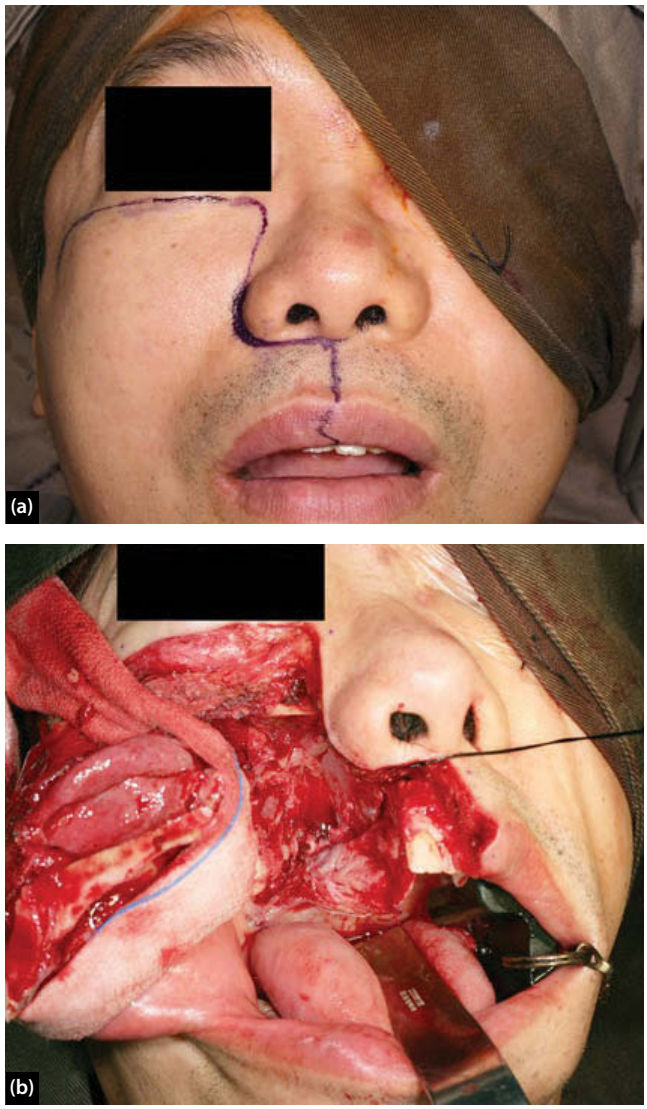

Figure 8.6 (a) Weber-Ferguson-Longmire incision for maxillary swing approach to the nasopharynx. (b) View of the nasopharynx after swinging the maxilla laterally.

Figure 8.6 shows the facial incision for the maxillary swing approach and view of the nasopharynx after swinging the maxilla laterally.

FACIAL TRANSLOCATION APPROACH – ANTERO-LATERAL APPROACH

An alternative approach is the facial translocation procedure. In this approach, the whole maxilla, including the floor of the orbit, lateral orbital rim, malar prominence and zygomatic arch, is removed. Part of the coronoid process is also removed to provide exposure to the infratemporal fossa and masticator space. The maxilla is detached from the cheek flap and is replaced back to the facial skeleton as a free bone graft, secured with titanium plates. Hao et al report in a 53-patient cohort using this approach a 5-year local control rate of 53.6% and a 5-year overall survival rate of 48.7%, comparable to the maxillary swing approach.[94] The facial translocation approach has better

lateral exposure than the maxillary swing approach at the expense of jeopardizing the blood supply to the maxilla bone. This lateral exposure is usually not required in small recurrent tumours in the nasopharynx and a maxillary swing approach should suffice for resection of most locally recurrent NPC.

LATERAL SKULL BASE APPROACH – LATERAL APPROACH

This approach is based on neurotological principles.[95] Via an extended post-auricular incision, the external auditory canal is closed as a blind sac and the whole auricle is retracted anteriorly with the flap. An extended mastoidectomy and total parotidectomy are then performed to allow the rerouting of the facial nerve. The zygomatic arch is removed and the temporalis muscle is then divided so that the base of the middle cranial fossa can be accessed. To improve the exposure, the condylar process of the mandible can be removed. The mandibular branch of the trigeminal nerve has to be divided and the pterygoid muscles removed from the attachment to the lateral pterygoid plate. The internal carotid artery is then identified and retracted. The tissue in the parapharyngeal space including the cartilaginous Eustachian tube can be resected *en bloc* with the tumour in the nasopharynx.

The advantage of this approach is the early identification and protection of the internal carotid artery. The major disadvantage is the extent of mobilization of normal tissues that needs to be performed to expose the tumour and subsequent morbidity. The visualization of the midline of the nasopharynx and access to resect lesions extending anteriorly to the nasal cavity and paranasal sinuses is poor. Of the 13 patients treated with the approach by Fisch et al, six patients with small recurrences had good local control.[96] Few other reports exist of the use of this approach for resecting recurrent NPC, given that other simpler approaches provide more direct exposure.

ENDOSCOPIC APPROACH

Endoscopic endonasal approach to the anterior skull base is now an established surgical approach to resect tumours in the nasal cavities, paranasal sinuses and anterior skull base.[97] Employing the endoscopic approach to resect nasopharynx tumour is a natural extension of application. Since the first decade of the 21st century, several case series on using the endoscopic approach to resect recurrent NPC have been published. Most of the cases were small tumours with short follow-up periods. The oncological results of endoscopic nasopharyngectomy are respectable, with most series having a 2-year local control of over 80%.[98] The endoscopic approach causes no damage to normal structures of the facial skeleton and minimal loss of function.

An extension of the endoscopic approach is the application of the da Vinci surgical robot (Intuitive Surgical Inc., Sunnyvale, USA) to assist the minimally invasive nasopharyngectomy. The da Vinci surgical robot has been successfully applied to resection of early oropharyngeal, laryngeal and hypopharyngeal cancers. The advantages of the surgical robot include 3D optics, superior manipulation of surgical instruments in tight space, motion scaling and tremor filtration. The nasopharynx is a confined space and endoscopic surgery suffers from lack of space for triangulation of instruments. The da Vinci surgical robot can allow complex movements like suturing, blunt and sharp dissection to be performed in the confined space of the nasopharynx similar to open procedure. Ozer and Waltonen in 2008 first reported a cadaveric experiment on using the da Vinci surgical robot to perform nasopharyngectomy[99] and Wei and Ho in 2010 reported the first clinical case of robotic assisted nasopharyngectomy.[100] Tsang et al have reported a case series of 12 patients who underwent robotic assisited nasopharyngectomy and the 2-year local control was 86%, comparable to other endoscopic nasopharyngectomy series.[101] The advantage over open nasopharyngectomy included shorter hospital stay and less blood loss. **Figure 8.7** is a screen capture from the da Vinci surgical robot performing a robotic nasopharyngectomy.

SURGERY FOR NODAL FAILURES

The poor results and high complication rate for salvaging nodal failures with re-irradiation means alternative management options should be sought for treating nodal failures. Radial neck dissection is considered as the standard of care for management of nodal failures.[85] The rationale for performing radical neck dissection instead of a lesser operation is based on several clinical observations on nodal failures in NPC. First, there are usually multiple nodes that are involved in NPC, even if pre-operative imaging suggests only single-node involvement. Second, extra-capsular involvement is high, reported as high as 70% in one study.[102] As further radiation may not be possible, sparing structures like the internal jugular vein or sternocleidomastoid muscle may leave behind microscopic disease that would not receive post-operative radiotherapy. The spinal accessory nodes are frequently involved in

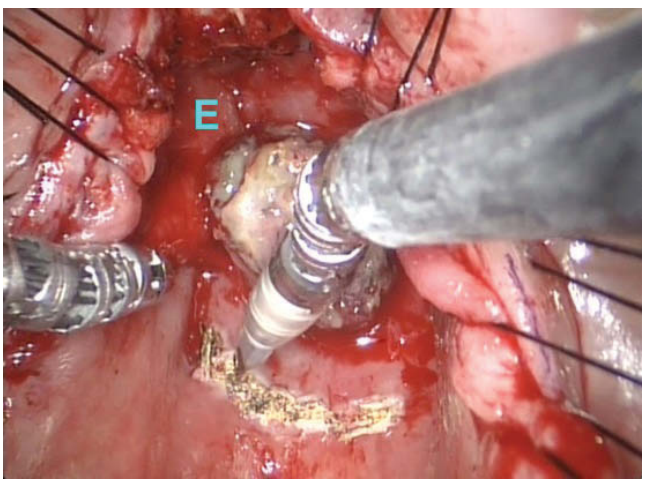

Figure 8.7 Screen capture from the da Vinci surgical robot performing robotic nasopharyngectomy. The soft palate was split in the middling to facilitate placement of the robotic arms.

NPC metastasis and together with the high risk of extracapsular spread, a type I modified radical neck dissection is still suboptimal. However, recent studies have shown that level I lymph nodes are rarely involved and can be spared in the neck dissection.[103]

For advanced nodal disease where the tumour may invade vital structures like the brachial plexus or fully encases the carotid artery at the skull base level, complete excision with sacrifice of these structures may not be advisable. If appropriate, surgery with palliative intent can be offered, as long as realistic goals for the procedure are set. The patient can then be prepared for brachytherapy with after-loading of radioactive source. Special plastic nylon tubes can be placed across the affected area 1 cm apart (**Figure 8.8**). The overlying skin should be removed as it may undergo necrosis after the re-irradiation. The skin defect can then be covered with an appropriate reconstructive option based on patient factors and the expertise available. After the completion of the brachytherapy, the plastic tubes can be removed at the bedside.

Salvaging nodal recurrent disease with radical neck dissection has a 5-year local control rate of 66% and 5-year overall survival of 37%.[104] In one series, the 5-year overall survival and 5-year local control for salvaging advanced nodal disease with radical neck dissection and brachytherapy were 72% and 48% respectively, comparable to less advanced disease treated with neck dissection only.

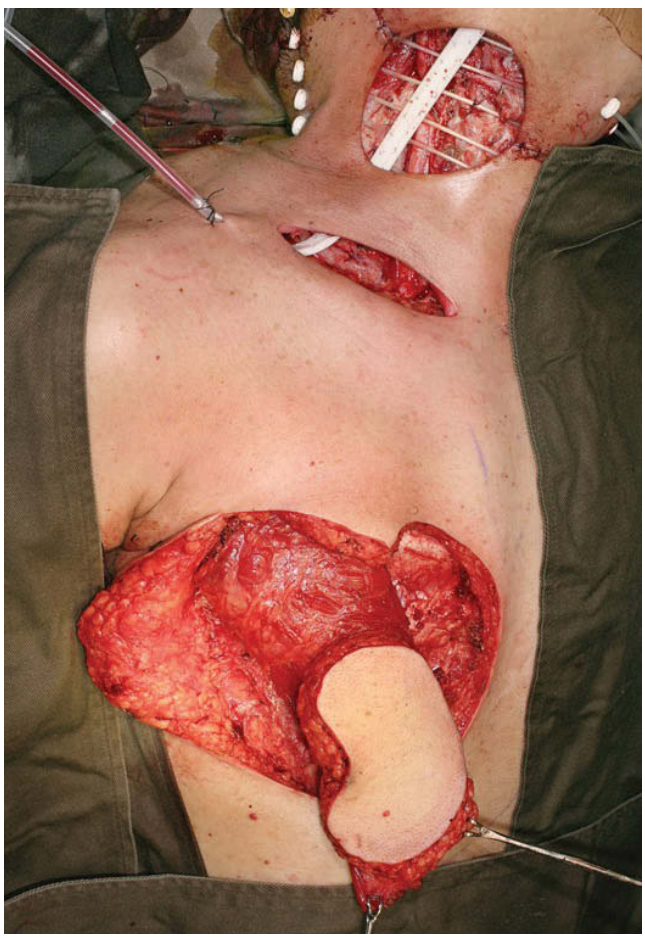

Figure 8.8 Salvage neck dissection for nodal recurrence in NPC. Plastic tubes were placed 1 cm apart for insertion of radioactive sources during brachytherapy. The overlying skin was involved and resected. A pectoralis myocutaneous flap was used to cover the defect.

TREATMENT OF METASTATIC DISEASE

Treatment for oligometastasis

Traditionally, distant metastases were not treated with surgery. With successful surgical resection and long-term survival for solitary metastasis from colon cancer, interest in curative treatment of distant disease in head and neck cancer has been renewed. A large single-centre review showed that 34% of patients with metastatic disease had single organ metastasis, and 16% with solitary metastasis at the time of diagnosis.[105] Options for treatment of oligometastasis include surgical resection, radiofrequency ablation and radiotherapy.[106–108] Although reports are usually case series and prone to selection bias, addition of curative treatment shows significantly better survival than chemotherapy alone in cases where the metastasis can be completely ablated. This area is now a focus of additional research and may redefine our current definition of incurable disease.

Chemotherapy for distant metastasis

Survival of over 6 months after development of distant metastasis was once considered a rarity. With increasing choice of new chemotherapeutic agents, there are now more options for continuation of palliative chemotherapy should one regimen fail. Traditional first-line chemotherapy for metastatic NPC is a combination of cisplatin and 5-florouracil and the medial overall survival is around 12 months. Second-line drugs include gemcitabine, docetaxel, capecitabine and paclitaxel. The newer agents have reported response rates of 50–70% and are well tolerated.[109] Palliative chemotherapy should be offered unless the patient's general condition is not fit.

PROGNOSIS

The treatment results of NPC have shown remarkable improvement in the last 40 years. The age standardized mortality rate for NPC in Hong Kong in 1983 was 9.8 per 100 000, dropping to 7.4/100 000 in 1993 and 3.0/100 000 in 2012. This threefold reduction in mortality is partly caused by 30% reduction in incidence but, more importantly, by the improvement in curative treatments. The two main reasons for improvement are the introduction of IMRT and concurrent chemoradiation as a standard of care in Hong Kong. Most contemporary studies report locoregional control rates of over 90% at 2–5 years and distant disease accounts for most failures. A large series from Hong Kong with more than 2600 patients showed a 5-year distant recurrence rate of 19%.[73]

Analyzing the survival, with the AJCC eighth edition stage classification, of more than 900 patients from 1998–2007 treated with 3D conformal radiation or IMRT with or without chemotherapy, Lee et al reported the 5-year disease-specific survival for stage I was 100%, stage II 90%, stage III 67%, stage IVA 67%, stage IVB 68% and stage IVC 18%.[110] This is a remarkable improvement as in the last edition of this book, the quoted 5-year survival for stage IVA-B was in the range of 20–40%.

COMPLICATIONS OF TREATMENT

Radical radiotherapy for NPC inevitably exposes normal tissue in the vicinity of the tumour to a damaging dose of radiation. Acute, subacute and late complications are well recognized and reported in the literature. A useful source of information on the subject can be obtained from the comprehensive review of Lee.[111]

As the mucosa of the head and neck region is the radiation volume, mucositis of the oral cavity, oropharynx and hypopharynx occurs to a varying degree during treatment. The mucositis can be severely aggravated if concurrent chemotherapy is given. Up to 90% of patients may need enteral feeding via a gastrostomy or nasogastric tube. Salivary function will be decreased during radiotherapy and depending on the dose to the major salivary glands, the salivary function may or may not recover. With IMRT, it is now possible to reduce the dose to the contralateral parotid gland in T1-T2 tumours and reducing the incidence of lifelong xerostomia.[112]

Otological complications frequently occur after radiation. OME, acute otitis media and otitis externa are common complications. The treatment of OME should be conservative as current evidence shows that the use of a grommet during or soon after radiotherapy is associated with a high incidence of persistent perforation and purulent otorrhoea.[113] Late complications of radiotherapy to the ears include sensorineural hearing loss and osteoradionecrosis of the temporal bone. A minor proportion of sensorineural hearing loss patients may lead to complete deafness but, fortunately, most can be salvaged by cochlear implants. Minor osteoradionecrosis of the external auditory canal can usually be managed conservatively with frequent cleaning and antibiotic ear drops. Significant osteoradionecrosis of the temporal bone can lead to deafness, facial nerve palsy and intracranial infection. The necrotic bone may need to be debrided and the defect covered with a local temporalis muscle flap or a vascularized free flap.[114, 115] With the introduction of IMRT and limitation of the radiation dose to the cochlea and temporal bone, the incidence of temporal bone complications are expected to reduce.[116]

Olfactory dysfunction, nasal crusting, rhinosinusitis and intranasal adhesions are common nasal complications. Olfactory dysfunction, usually transient, occurs in quite a number of patients towards the end of radiotherapy and slowly recovers over the next few months. Nasal crusting and symptoms of rhinosinusitis (thick nasal catarrh and foul smelling nasal discharge) are very common following radiotherapy. Regular saline nasal douching in the first few years after radiotherapy with courses of antibiotics may be needed for adequate control. Minor nasal adhesions between septal spurs and the nasal turbinates are quite common and need no treatment. Occasionally, marked scarring at or close to the choana (**Figure 8.9**) may occur, particularly in patients with more advanced local disease requiring a higher local dose of radiation through afterloading brachytherapy. These adhesions should be removed to facilitate future endoscopic assessment of the nasopharynx.

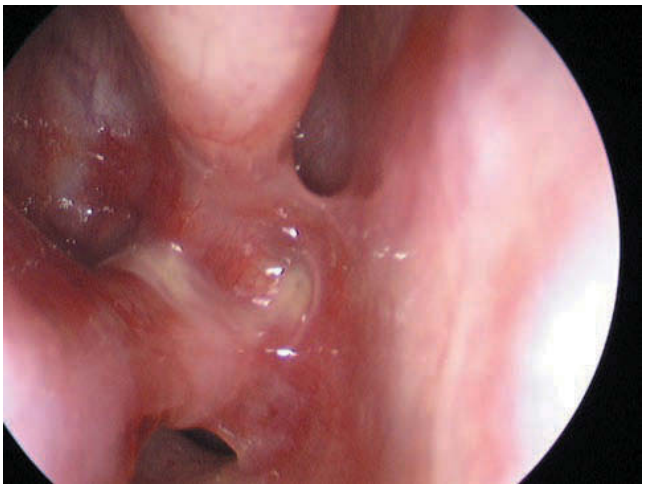

Figure 8.9 Early intranasal adhesions after radiotherapy as seen through a 0° rigid nasendoscope situated inside the right nostril. Note the adhesions around the posterior ends of the middle and inferior turbinates and the nasal septum.

The latent interval of late complications can vary from several months to many years after irradiation, owing to irreversible damage. Tissues that have poor powers of regeneration, such as sensory and neural tissues, are particularly prone. Apart from the total radiation dose, the dose fractionation and timing of delivery will affect the occurrence of late complications.

With the old 2D radiotherapy techniques, the reported incidence of late complication can be more than 30%.[117] Data on long-term complications with the modern IMRT is still lacking but as the dose to the normal tissue is reduced, hopefully we will see a reduction in the long-term complications in the future. On the other hand, the addition of concurrent chemotherapy increases the long-term toxicity of radiation. Swallowing problems in NPC patients treated with radiotherapy is very common and can occur early after treatment.[118] Late dysphagia can affect up to 50% of the head and neck cancer patients treated with concurrent chemoradiation[119] and this increase in late dysphagia is also seen in NPC patients.[120, 121] Dysphagia not only affects quality of life[122] but can also lead to life-threatening aspiration pneumonia.[123]

Radiation-induced fibrosis is another late complication that can lead to neck stiffness and trismus. Apart from osteoradionecrosis of the temporal bone, the skull base and mandible are also at risk for this complication.

Initial treatment including local debridement and hyperbaric oxygen is helpful, but some patients may need definitive resection of the involved bone segment and reconstruction with a free osteocutaneous flap. Osteoradionecrosis of the skull base and radiation fibrosis can lead to lower cranial nerve palsies.[124, 125] The differential diagnosis of late lower cranial nerve palsies is local recurrence and can be difficult to differentiate from osteoradionecrosis or post-radiation fibrosis. Hypothalamic-pituitary dysfunction may result in a range of hormonal deficiencies requiring lifelong replacement therapy. The symptoms and signs of hormonal dysfunctions are subtle and require a high index of suspicion for their diagnosis. Temporal lobe necrosis can develop in patients that were treated with the old radiation techniques but, with modern IMRT, the dose to the temporal lobe is minimal, unless it is for re-irradiation. The symptoms and signs of temporal lobe necrosis are subtle, including personality changes, memory loss and loss of cognitive function. The overt cases may present with epileptic attacks and the more severe cases with symptoms and signs of raised intracranial pressure.

Radiation-induced malignancies mostly develop beyond 5 years after radiotherapy and occur in around 0.3–3% of patients. Radiation-induced malignancy is more important in NPC than other head and neck cancers as patients are younger and coupled with the high cure rate, more patients can survive long enough to develop a radiation-induced cancer. Radiation-induced malignancies can be broadly divided into mucosal squamous cell carcinomas and radiation-induced sarcomas. Unlike atomic bomb survivors, radiation-induced thyroid malignancy is rare in NPC patients. Mucosal squamous cell carcinoma commonly can occur in the edge of the radiation field, including the external auditory canal, middle ear, paranasal sinuses, oral tongue, oropharynx and hypopharynx. It can also occur in the nasopharynx, which needs to be differentiated from local recurrence. Radiation-induced sarcomas are often of the fibrosarcoma or osteosarcoma subtype and usually occur in patients who have received a high dose of radiation. Radiation-induced sarcomas are often difficult to diagnose and can be confused with radiation fibrosis or radionecrosis.[126] Curative resection with clear margins is still the best treatment for radiation-induced malignancies. The prognosis of radiation-induced malignancy is often poor due to the delay in diagnosis, inability to deliver further multimodality treatments and poor performance status of the patients as they suffer from other complications of radiation.[127]

Internal carotid artery aneurysm is a rare life-threatening complication after radiotherapy for NPC. The typical patient will present with minor sentinel bleeds followed by massive epistaxis a few hours to a few days later. Treatment includes prompt airway control followed by endovascular stenting of the internal carotid artery to exclude the aneurysm or ligation of the affected internal carotid artery with vascular bypass. A high index of suspicion is required to diagnose the condition before the patient develops massive rupture of the aneurysm.[128]

CONCLUSION

NPC is a unique disease with a highly variable geographical distribution, distinct viral aetiology interplaying with individual genetic susceptibility and environmental carcinogens. The last two decades have seen a remarkable advance in the treatment in all fronts; from 2D radiation to IMRT, single agent chemotherapy to targeted therapy and open surgery to endoscopic resection. Future developments in in the basic science of the disease include a vaccine for EBV, better understanding of the molecular genetics and newer tumour markers for screening and monitoring of the disease. Newer radiotherapy techniques including image-guided radiotherapy, adaptive radiotherapy and proton radiotherapy are available and may become the mainstream treatment modality. Technological advancements may enable surgeons to perform more endoscopic or robotic surgeries as salvage, reducing the morbidity from open resection.

BEST CLINICAL PRACTICE

- ✓ Nasopharyngeal biopsy under endoscopy should be the first and definitive investigation to establish the diagnosis.
- ✓ NPC is highly radiosensitive; radiation is the first-line treatment for all primary NPC.
- ✓ Radiation delivered in the form of IMRT with up to 66–72 Gy to the gross tumour and involved lymph nodes. 60 Gy of radiation should be given to clinically negative cervical lymph nodes. IMRT will enable delivery of adequate radiation to target the tumour while reducing the radiation dose to adjacent normal structures.
- ✓ Radiation with concurrent chemotherapy is the gold standard for more advanced disease, including stage II disease with bulking lymph nodes and all stage III and stage IV diseases. Cisplatin, delivered either weekly at 40 mg/m^2 or 3-weekly at 100 mg/m^2, is the gold standard.
- ✓ Patients should be followed up regularly after treatment to detect recurrence and complications from treatment.
- ✓ Salvage surgery should be considered for local or regional recurrence as surgery can spare the significant morbidity from re-irradiation.
- ✓ Effective new chemotherapeutic agents are now available for patients with disseminated disease and can offer useful palliation and prolong overall survival.

FUTURE RESEARCH

- The exact role of EBV in the carcinogenesis of endemic form of NPC.
- What are the exact genetic factors in the carcinogenesis of NPC and can these genes be used to define high-risk patients?
- Can the development of a successful EBV vaccine reduce future NPC development in an endemic population?
- What is the best strategy to deploy a mass-screening programme in endemic areas that is cost-effective and improves treatment outcome?
- How can long-term morbidities from chemoradiation, especially in terms of late dysphagia, be further minimized? Can we further reduce the radiation dosage to normal tissue without jeopardizing disease control?
- What is the role of minimally invasive surgeries like endoscopic surgery and robotic surgery in salvaging local recurrence?
- The development of target therapy and newer chemotherapeutic agents with similar or better efficacy than the current line of chemotherapy but with less toxicities.

KEY POINTS

- Nasopharyngeal carcinoma is unique among all head and neck cancers because of wide geographical and ethnic variation in incidence rates. The annual incidence rate in areas with high prevalence of the disease can be up to 50 times higher than low prevalence areas.
- The highest incidence is found in Southern China, including Taiwan, Hong Kong and Macau. Migrants originating from high incidence areas also have a high incidence of developing NPC, though the risk decreases in second or third generation migrants.
- Populations from Malaysia, Indonesia, Arabia, North Africa, Thailand and the Philippines, and Inuits (from Canada and Greenland), have intermediate incidence of NPC.
- Caucasians and populations from Northern China and East Asia (Japan and Korea) have a low incidence of NPC.
- The commonest histological form of NPC in an endemic area is the poorly differentiated type or undifferentiated type (WHO types II and III). The endemic form of the cancer is associated with EBV, and EBV genomes are found in all cancer cells.
- The peak incidence of NPC is around the fourth to fifth decade, a decade earlier than other head and neck squamous cell carcinoma.
- Consumption of salted fish and preserved foods, especially at a young age, are considered as aetiological factors. Smokers also have a moderate increase in risk.
- The aetiology of NPC is the result of a complex interplay of genetic factors, early latent infection by EBV and its subsequent reactivation and exposure to environmental carcinogens. The carcinogenesis of NPC is probably a multistep process.
- Serum EBV IgA antibiodies against viral capsin antigen (VCA), early antigen (EA) and Epstein—Barr nuclear antigens (EBNA) are elevated in patients suffering from NPC and can be used as a tumour marker for screening the cancer. These serological markers are not useful for monitoring of treatment efficacy and screening for recurrence.
- Plasma EBV DNA is a more sensitive and specific tumour marker for NPC. It is also useful for prognostication, monitoring of treatment response and screening for tumour recurrence.
- Symptomatology of NPC can be vague, easily ignored and confused with other conditions. Physical examination often cannot pick up the diagnosis. A high index of suspicion is required to avoid delaying the diagnosis, especially if the patient ethnicity is from an endemic area.
- The most common complaint at presentation is the presence of upper neck swelling: unilateral neck swelling is most common, but bilateral neck metastases are not infrequent. Cervical lymphadenopathy is the presenting complaint in almost 50% of patients. A significant proportion of patients presenting with other complaints also have cervical lymphadenopathy on examination.
- 30% of patients present with nasal symptoms, including blood-stained nasal discharge, nasal obstruction, postnasal drip or even frank epistaxis.
- Approximately 20% of patients present with aural symptoms, including deafness, tinnitus and otalgia. A retracted tympanic membrane or OME is a very common clinical finding. This finding usually correlates with the side of the nasopharynx that has bulkier disease. Adult patients with unexplained unilateral persistent OME should be screened for the presence of occult NPC.
- Neurological complaints include headaches or cranial nerve symptoms. Headaches are a common complaint, occurring in almost 20% of patients, but they may be referred pain when distal branches of the trigeminal nerve are invaded by the tumour in the nasopharynx or nose. However, they can also be the result of bony erosion of the skull base. Cranial nerve symptom(s) may be isolated or multiple. In either case, it occurs late in the disease from the spread of the tumour through the foramina of the base of the skull or with parapharyngeal involvement of the last four cranial nerves. Cranial nerves V and VI are the most commonly involved. When cranial nerves III–VI are affected together, cavernous sinus involvement is the cause. Horner syndrome is rare, but if present is typically accompanied by paresis of one or more of the last cranial nerves.
- MRI is the imaging of choice for delineating the extent of disease in the skull base. CT scan is useful in detecting cortical bone erosion in the skull base but cannot often differentiate between normal structures and tumour invasion in the skull base. PET CT is a useful adjunct to delineate the extent of disease, nodal metastasis and distant metastasis.
- The nodal staging of NPC is different from other head and neck squamous cell carcinoma. The number of lymph nodes involved is not considered in the nodal staging. The laterality (bilateral = N2), size (>6 cm) and inferior location (extends below caudal border of cricoid cartilage) are the considerations in nodal staging.

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CHAPTER 9

BENIGN SALIVARY GLAND TUMOURS

Jarrod Homer and Andrew Robson

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SEARCH STRATEGY

Data in this chapter may be updated by a Medline search of publications that focused on the pathology, aetiology and management of benign salivary gland tumours.

INTRODUCTION

There are a number of important issues to address in patients with tumours of the major salivary glands. Accurate and rapid pre-operative diagnosis is imperative, in order to diagnose malignancy. There is some controversy in the choice of correct operation of the commonest type and location of tumour: a pleomorphic adenoma of the parotid gland. The anatomical relationship of a tumour to the facial nerve (or branch) in the parotid gland is nearly always intimate and the potential for a catastrophic cosmetic handicap can make surgery challenging. In is interesting to observe that, whist there has been a great deal of commentary regarding adequate workload in, for example, thyroid surgery, there has been almost none regarding parotid surgery; and yet the consequences of suboptimal surgery that includes incomplete tumour resection and facial palsy are potentially catastrophic for the patient.

In this chapter, these issues and others are addressed and guidelines for the management of benign salivary gland tumours are established.

EPIDEMIOLOGY AND DISTRIBUTION

Bradley and McGurk[1] analyzed the incidence of salivary gland tumours in a defined population in Nottinghamshire, UK between 1988 and 2007. They reported an incidence of benign parotid neoplasms of 5.3–6.2 per 100 000 population and 0.5–0.55 per 100 000 of benign submandibular tumours. The distribution between sites conformed to the traditional teaching of approximately 80% within the parotid gland, and 10% within the submandibular and minor salivary glands respectively. From these data, there does not appear to be a change in annual incidence of benign salivary gland tumours over the 20-year reporting period in the paper.[1]

All age groups are affected with a peak incidence in the sixth decade. There is a female preponderance, with the exception of Warthin's tumours, which are more common in males.[2]

Table 9.1 compares information from Bradley and McGurk[1] (1065 cases including malignant tumours) with a 1985 publication of British Salivary Gland Tumour data of 2410 cases.[2]

The distribution between histological types is shown in **Table 9.2**.

TABLE 9.1 Frequency of epithelia salivary gland tumours and malignancy analyzed by site

	Benign vs malignant (%)	
Site	**Eveson & Cawson[2]**	**Bradley & McGurk[1]**
Parotid	85	91
Submandibular	64	75
Sublingual	14	0
Minor glands	54	60

TABLE 9.2 Histological types of benign tumour by site in a Nottingham population 1988–1997 and 1998–2007

	Major salivary glands						Minor glands		Total		
	Parotid		Submandibular		Sublingual						
	88–98	98-07	88–97	98–07	88–97	98–07	88–97	98–07	88–97	98–07	Cumulative
Pleomorphic adenoma	275	263	31	36	–	–	28	18	333	318	651
Warthin's tumour	100	100	2	1	–	–	–	–	102	101	203
Oncocytoma	3	6	1	0	–	–	–	–	4	6	10
Monomorphic, NOS	9	0	1	0	–	–	–	–	10	0	10
Basal cell carcinoma	6	13	1	0	–	–	–	2	7	15	22
Canalicular adenoma	–	–	–	–	–	–	3	3	3	3	6
Cystadenoma	3	0	–	–	–	–	1	–	4	0	4
Myoepithelioma	1	5	–	–	–	–	–	4	1	9	10
Fibromyoma	–	–	–	1	–	–	–	–	0	1	1
Lipoblastoma	–	–	–	2	–	–	–	–	0	1	1
Total	397	387	36	36	–	–	32	27	464	454	918

AETIOLOGY

Whilst radiation can induce malignant salivary gland tumours, the evidence that it can induce benign tumours is much weaker; restricted to a possible association with Warthin's tumours.[3] In recent years, public concern has focused on the use of mobile telephones and the development of regional malignancies, induced by electromagnetic fields. However, there is no evidence of an increased risk of salivary gland tumours.[4] It has been speculated that human papillomavirus 16 (HPV16) may be associated with pathogenesis of benign salivary tumours, but there is no convincing evidence for such.[5, 6]

PRESENTATION

Most parotid and submandibular gland tumours grow slowly over a long period of time without causing symptoms. A very small number cause discomfort by obstructing salivary flow. Most benign tumours will be smooth, relatively mobile and painless to palpate. The following symptoms and signs suggest the tumour may be malignant or be undergoing malignant transformation:

- pain
- paraesthesia (especially adenoid cystic carcinoma)
- rapid growth or an increase in rate of growth
- facial nerve palsy/other nerve palsy
- skin involvement
- fixity
- irregularity.

A further consideration is the age of the patient and the site of the tumour. Malignancy is relatively more likely in younger patients and in submandibular tumours (40% malignant).

The patient with a parotid tumour eventually becomes aware of a firm mass that is steadily getting bigger behind the angle of their jaw in the retromandibular region, in front of the tragus or in the cheek (**Figure 9.1**). Deep lobe parotid and parapharyngeal space tumours may displace the tonsil and palate medially and are often impalpable

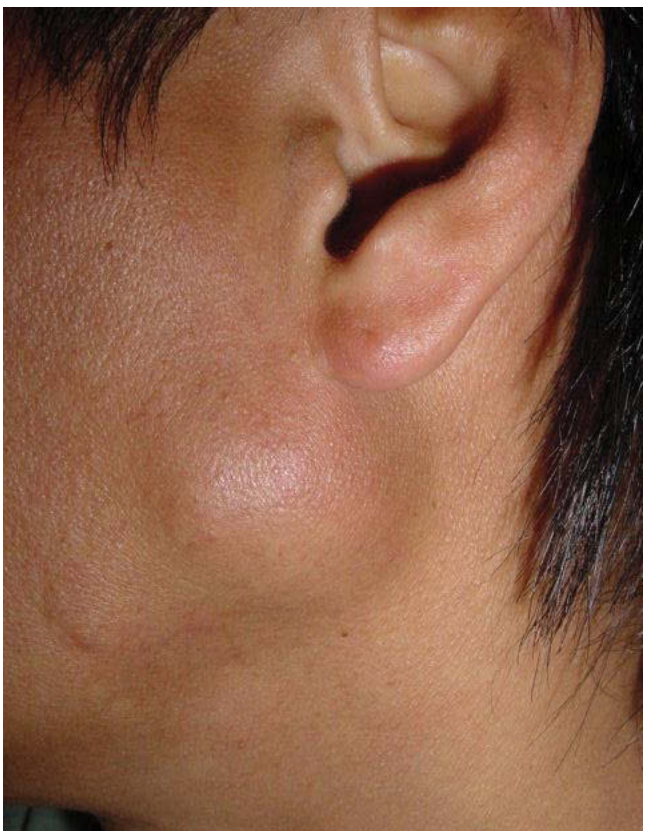
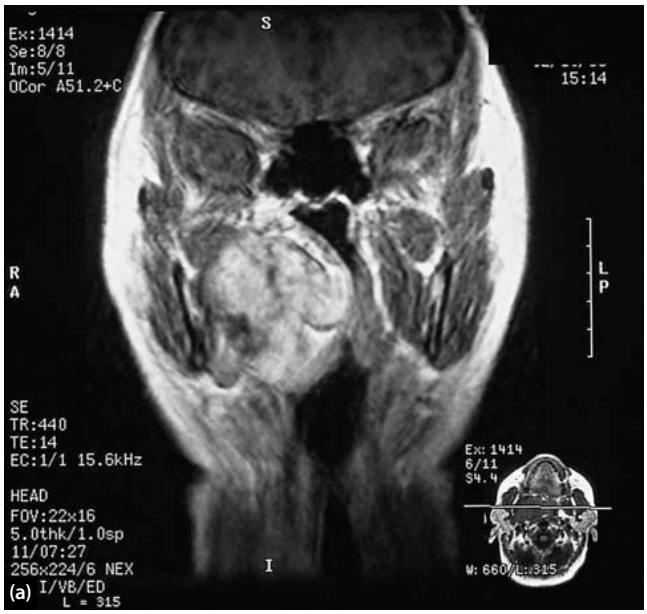


Figure 9.1 Typical presentation of a pleomorphic adenoma of the parotid gland, a retromandibular swelling.



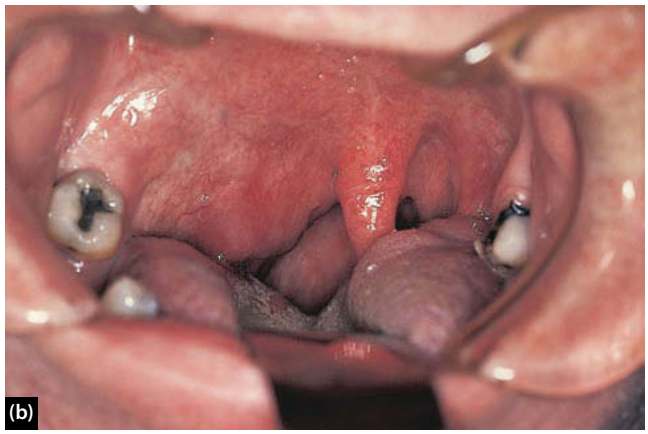


Figure 9.2 **(a)** MRI of a very large deep lobe parotid tumour that had caused Eustachian tube dysfunction, altered the quality of voice and resulted in obstructive sleep apnoea; **(b)** typical intraoral appearance of a deep lobe tumour with medial displacement of the right tonsil.

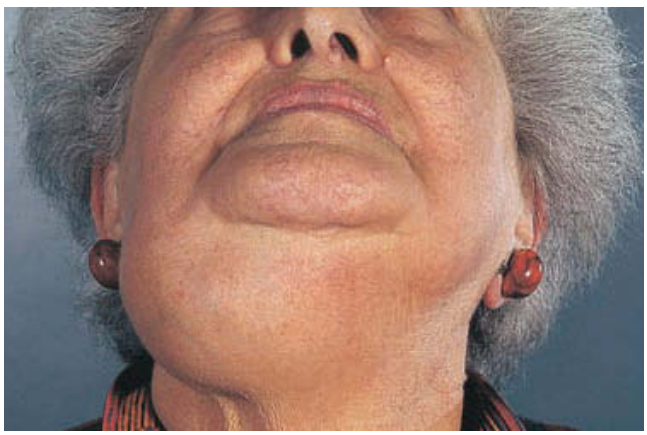


Figure 9.3 A pleomorphic adenoma of the submandibular gland presenting as a swelling in the submandibular triangle.

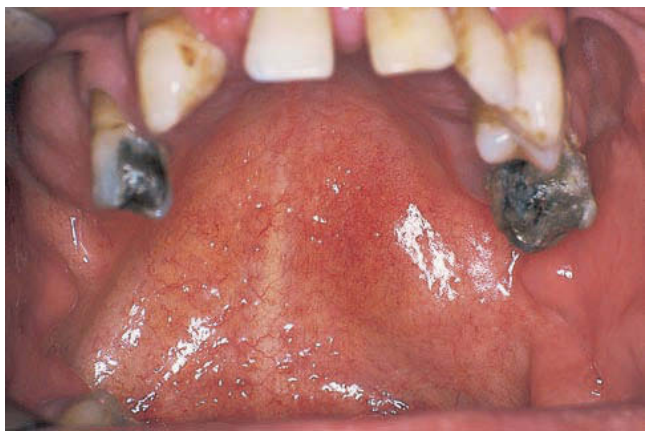


Figure 9.4 Unilateral swelling of the left side of the palate, typical of a minor salivary gland tumour.

from outside. Very large parapharyngeal salivary tumours cause stertor, sleep disordered breathing, affect the quality of the patient's voice and may even interfere with Eustachian tube function (**Figure 9.2**). Increasing numbers of salivary gland tumours are being detected as incidental findings on CT, MRI and PET-CT scans performed for other indications. These tumours are asymptomatic and their management poses unique challenges.

Tumours arising in the submandibular gland present as swellings in the submandibular triangle which can be sometimes localized more accurately by bimanual palpation of the floor of the mouth (**Figure 9.3**). It is sometimes difficult to differentiate a tumour arising in the posterior aspect of the submandibular gland from one that is in the tail of the parotid gland and, in turn, either can be mistaken for a lymph node. Benign tumours in the minor salivary glands of the oral and pharyngeal mucosa present as firm submucosal swellings (**Figure 9.4**). Ulceration is rarely if ever seen unless there has been local trauma and, in the absence of that, malignancy should be suspected.

INVESTIGATION

Imaging

In general, every patient with a major salivary gland tumour requires some form of imaging. The arguments for routine imaging are:

- Ultrasound scan can be done at the time of fine-needle aspiration cytology (FNAC), ideally in the setting of a neck lump one stop clinic. FNAC is more accurate if ultrasound-guided.
- Diagnostic information to complement FNAC; if FNAC suggests benignity, imaging may or may not be commensurate with this. If not (i.e. benign cytology but imaging shows, for example, an irregular margin), the cytology should either be repeated and/or the excision performed sooner rather than later.
- If the FNAC is non-diagnostic, imaging may assist in diagnosis and plan urgency of resection.

- If FNAC is non-diagnostic or false negative, and tumour is then found to be malignant, the imaging performed pre-operatively will help to stage the tumour and plan further treatment if necessary.
- Distinguishing:
  - a parotid lump from either high-level 2 lymph node
  - a parotid lump from diffuse parotid enlargement
  - a submandibular lump from an adjacent level 1 (anterior) or level 2 (posterior) lymph node
  - a submandibular tumour from a tumour of the tail of parotid.

Ultrasound imaging can be performed at the time of an initial clinic visit, and fulfils most of the requirements of imaging.[7] It can also demonstrate sialolithiasis and sialectasis very clearly. However, axial (MR or CT) should be performed under the following circumstances:

- tumours that are large (e.g. > 3 cm)
- deep lobe/parapharyngeal space involvement (note that an ultrasound scan may well miss a 'dumbbell' (**Figure 9.5**) tumour in which the greater component of the tumour lies in the parapharyngeal space)
- suspicion of malignancy.

MR is generally preferred because it gives better definition of tumour–normal salivary gland interface.[8] It also is not affected by dental artefact.

Imaging features (on any modality) that suggest malignancy include an irregular capsule, or extracapsular invasion, hypervascularity and imaging features consistent with necrosis.

Fine-needle aspiration cytology and needle core biopsy

Malignant tumours must be detected pre-operatively wherever possible because the staging, workup and surgery may differ. Most salivary gland tumours are investigated by FNAC, at least initially. The accuracy for the diagnosis of benignity or malignancy in most large series is around 80–90%[9, 10] and on systematic review, and concordance with histology for 80% in cancers and 95% in benign tumours.[11] The accuracy will vary from centre to centre. The use of core biopsy can improve the accuracy of diagnosis further. Whilst more invasive, there is no evidence that there is a greater chance of tumour seeding with core biopsy.[12] Some authors advocate the use of core biopsy primarily instead of FNAC. An alternative view is to use core biopsy as a second-line investigation, or when FNAC shows possible malignancy. Such a protocol has been shown to give rise to a sensitivity of 100% and specificity of 92%.[13] The use of ultrasound (a) increases FNAC and core biopsy 'hit rate' and (b) gives useful diagnostic information.[7]

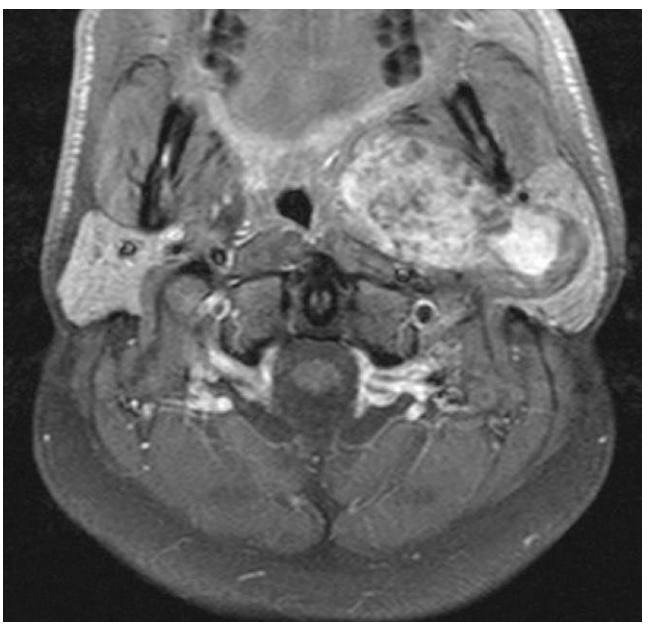


Figure 9.5 MR scan of dumbbell tumour.

THE MANAGEMENT OF COMMON BENIGN TUMOURS

Pleomorphic adenoma

Most patients with a pleomorphic adenoma should be offered and advised to have surgery on the basis of:

1. definitive histology
2. continued growth if left untreated
3. small chance of malignant transformation (see below).

Most parotid pleomorphic adenomas are within the superficial lobe but a small but significant proportion arise either within the deep lobe or involve it by direct growth. Pleomorphic adenomas, left untreated for many years, can attain a large size (**Figure 9.6**). Pleomorphic adenoma can also arise from accessory parotid tissue along the line of the duct (**Figure 9.7**). If far enough anteriorly in this area, they then may only be visible when the mouth is opened and the tumour is pushed outward by the forward movement of the coronoid process of the mandible. Pleomorphic adenomas can also arise in the submandibular gland, or minor salivary glands (e.g. soft palate, see **Figure 9.4**).

The firmness of these tumours varies with the nature and amount of the stromal component and thus ranges from soft, in the case of the more mucinous tumours to hard in the case of tumours with an extensive chondroid or collagenous component.

The myxoid stroma of pleomorphic adenomas is one of its most characteristic features. It can form the major part of the tumour and can bulge into the normal gland parenchyma without any capsule intervening. The almost mucoid nature of many pleomorphic adenomas makes them extremely fragile so that they can rupture at operation. Rupture of the tumour inevitably seeds the operative field and significantly increases the chance of later recurrence.

The cartilage of pleomorphic adenomas, though often termed 'pseudo-cartilage', does not appear distinguishable in any way from true cartilage. Calcifications or bone

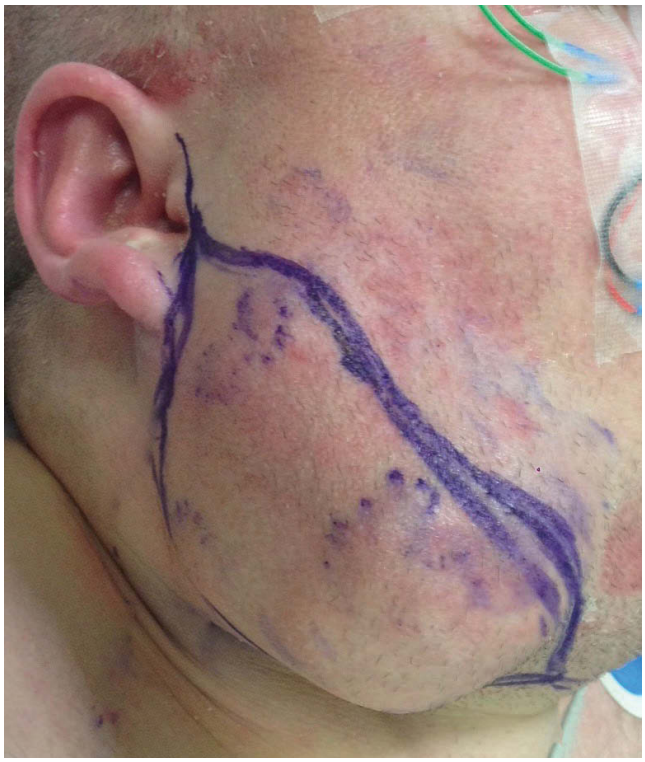


Figure 9.6 A large pleomorphic adenoma.

formation are unlikely to develop in any other salivary gland tumour and may be seen clearly in scans. Their presence in a salivary gland or a parapharyngeal mass strongly suggests that the tumour is a pleomorphic adenoma.

It is widely accepted that pleomorphic adenomas are derived from intercalated duct and myoepithelial cells which differentiate into epithelial and connective tissue structures. The epithelial cells are interspersed by stromal elements. Squamous metaplasia with keratinization is common and does not imply malignant change.

It is critical to understand that, in virtually all pleomorphic adenomas, the capsule is exceptionally thin (<20 micron) in at least one area and incomplete in about 50%, more so in the mucoid type which are therefore much more prone to potential spillage during surgery.[14]

The relevance of this and the choice of operation is discussed in the next section.

Another critical feature that influences management is the risk of malignant change. It has always been known that a small percentage of pleomorphic adenomas can undergo malignant transformation. The risk is essentially unknown in terms of x% over y years and historically a figure of about 1–5% in 10 years has been adopted. However, it is known that that only 0.15% of pleomorphic adenomas have features of malignant change[15] and so the actual risk of transformation is probably very low.

CHOICE OF OPERATION

Pleomorphic adenomas of the submandibular gland are treated with excision of the gland. This should be extra capsular and, as a result, there is a higher rate of marginal mandibular facial nerve injury.[16] Pleomorphic adenomas

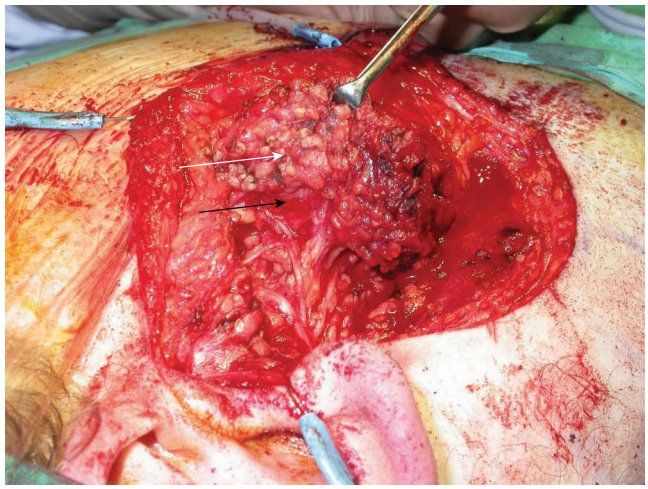


Figure 9.7 Despite taking a cuff of normal tissue, at least one aspect of the tumour capsule is adjacent to the facial nerve/branch. Partial parotidectomy with cuff. White arrow shows cuff but note black arrow show that narrowest margin is capsule only where tumour is adjacent to buccal branch of facial nerve.

of the minor oral salivary glands is treated by wide local excision.

The controversy in management of these tumours largely applies to the parotid gland. As a result of poor encapsulation and a tendency to rupture during resection, enucleation frequently results in subsequent recurrence and is an unacceptable historic practice. However, there is controversy regarding the extent of parotidectomy, from total superficial parotidectomy, through to a partial superficial parotidectomy (the tumour and a cuff of normal tissue) through to extracapsular dissection. The most common practice in the UK is partial superficial parotidectomy.[17]

The key theoretical argument for taking a cuff is the incomplete and thin capsule. However, most tumours, with the exception of very small tumours at the tail of the parotid, will be near the facial nerve or a significant branch thereof. This is the point demonstrated in **Figure 9.8**, i.e. there will almost always be one margin in which the tumour capsule is next to a facial nerve branch, no matter what type of operation is performed. Indeed, histological analysis shows that, even with 'standard' superficial parotidectomy, 81% had some degree of capsule exposure and this was >50% of the surface in 60%.[18]

Therefore, a less invasive approach using careful extracapsular dissection, when possible, can be justified on that basis. The majority of evidence shows at least similar rates of recurrence and facial nerve injury, with many showing lower rates of these complications and others.[19–21] These findings are not universal, but it should be noted that much evidence to the contrary involves analysis of very old data (e.g. going back to the 1960s–1980s).

If there is to be a cuff, there is no consensus as to the amount required. Many surgeons, in effect, will compromise between the two approaches, taking a narrow cuff (e.g. 1 cm) around the tumour. There is not much point in taking a large cuff e.g. a 'superficial' parotidectomy when at least one margin is likely to be negligible next to a nerve branch (see **Figure 9.8**).

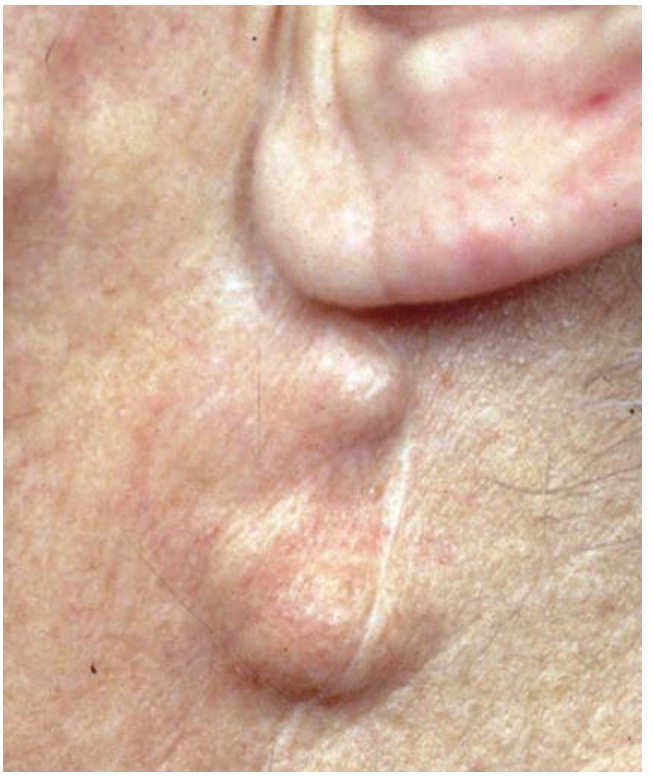


Figure 9.8 Clinical photograph showing recurrent pleomorphic adenoma presenting as multiple nodules. Note the scar from the previous surgery.

The salient argument arguments in favour of each approach are shown in **Table 9.3**.

DEEP LOBE TUMOURS

Deep lobe tumours generally require total conservative parotidectomy. However, for some smaller tumours, access via a limited superficial partial parotidectomy may facilitate an approach to the tumour inferior to the facial nerve, mobilizing just the inferior branches to access the tumour in order to perform an extracapsular dissection. This is the same approach (cervico-parotid) as for parapharyngeal tumours (which may include the deep lobe), except that division of the digastric muscle and styloid process ligaments may not be required.

PARAPHARYNGEAL SPACE PLEOMORPHIC ADENOMAS

These can be excised via a cervico-parotoid approach or, if too big and too anterior for this, via a transmandibulotomy/ transpharyngeal approach. Transoral robotic surgery offers an alternative approach, especially instead of the latter, and can be combined with a cervical approach if necessary.[22]

RECURRENCE OF PLEOMORPHIC ADENOMA

The overall recurrence rates of pleomorphic adenomas are in the region of 2% and occur typically about a decade after original surgery,[20, 23] although data from a Dutch national pathology database showed a 6.7% recurrence rate over 20 years.[15] Most recurrences are multi-centric (see **Figure 9.8**). A number of recurrences arise as a result of previous per-operative rupture or spillage of the tumour and seedlings may have been spread over a wide area, although this is probably much less the reason for recurrence than has been previously been cited anecdotally.[24]

An MR scan is the imaging of choice, both to characterize the identified recurrence(s) and detect further foci. It will also determine how much parotid tissue has been left behind after the primary surgery (which will often have been done in another institution).

Assuming the recurrence is still benign, the key issue for the surgeon to assume that this represents the last good opportunity for 'cure' with a good chance of facial nerve preservation without radical salvage surgery. In general, all remaining parotid tissue should be resected with the recurrences and the resection should be carried out mindful that there is a small but significant chance of the recurrent tumour being malignant. The necessary skills that may be required include retrograde nerve branch dissection; identification of facial nerve in mastoid; and nerve repair and cabling by micro-anastomosis. In some cases with, for example, superficial recurrence(s) only, there may be a role for limited surgery of these on the basis that this may be preferable to the significant chance of facial

TABLE 9.3 Arguments in favour for extracapsular dissection and partial parotidectomy with cuff in the surgical treatment of parotid pleomorphic adenoma

Extracapsular dissection	Partial parotidectomy with cuff or superficial parotidectomy
Recurrence rates are the same in this method as in superficial parotidectomy	On histopathology, the tumour capsule is incomplete and tumour cells extend through into adjacent tissue. Therefore, a cuff of tissue is necessary to achieve microscopic clearance and reduce chance of recurrence
Less cosmetic deformity	If the histology demonstrates an unexpected malignancy then clearance may still be adequate (if a low-grade tumour)
Lower incidence of Frey's syndrome	
There is no possible cuff in the tumour adjacent to one significant facial nerve branch in most cases	Dissecting close on the capsule may cause rupture (although when this does happen, it tends to be when dissecting capsule off facial nerve branch (i.e. no scope for a cuff here anyway)
If revision surgery is required (e.g. malignant on histopathology) then the tissue planes used to dissect and identify the main facial nerve and some braches are virginal	

nerve injury that may be inherent in formal revision parotidectomy surgery.

After a comprehensive resection, consideration of postoperative radiotherapy should be given. Radiotherapy is effective in reducing further recurrence of pleomorphic adenoma.[25]

It should be also emphasized that there is a much higher chance of malignant change within recurrent tumours, about 3%.[15] In the assessment, it is essential to

- repeat the FNAC (do not rely on the original histology)
- formally image with MR (mandatory regardless because of possible multifocality)
- get the original histology reviewed by a head and neck pathologist.

Further surgery for a second recurrence after radiotherapy is challenging in terms of minimizing morbidity and will be for disease which is, by definition, aggressive. Fortunately, these cases are rare but might include temporal bone resection, mandibulectomy and reconstruction for the resultant tissue defects as well as facial nerve reconstruction or reanimation (see **Figure 9.10**). This underlies the importance of aggressive treatment of recurrent disease at a point when it can be done in a non-mutilating fashion (i.e. at the first recurrence).[26]

Recurrent tumours of the submandibular gland should be treated with a selective neck dissection (1–3), which will remove the soft tissue that harbour recurrent disease.[16]

The management issues in recurrent disease are not straightforward and involve a working relationship between surgeon, pathologist and radiation oncologist – an example of benign disease that should be managed by a head and neck cancer multidisciplinary team.

Warthin's tumour

This tumour is also known and referred to as either adenolymphoma or papillary cystadenoma lymphomatosum. The latter terms are slightly ambiguous and tend not to be used. It accounts for 20% of benign parotid tumours. It is rare outside of the parotid gland.

The peak incidence of Warthin's tumours is in the seventh decade. Formerly, it was thought that these tumours predominantly developed in men, series quoted a 10:1 incidence ratio. More recent series suggest that this was either a misconception or that the sex distribution is becoming more equal with a male:female ratio of just 1.6:1.[27] There is a strong association between the development of Warthin's tumours and smoking and secondly a racial association in that it is comparatively rare in afro-caribbeans.[28, 29]

Warthin's tumours are comprised of lymphoid stroma and oncocytic epithelium. The lymphoid stroma suggests it arises from intra-parotid or peri-parotid lymph nodes, explaining why it is so rare in the submandibular gland, which contains no lymphoid tissue.

There is some controversy as to the exact nature of Warthin's tumours. Some studies have suggested a polyclonal origin for the epithelium, which would suggest a non-neoplastic origin for these lesions. This has led to a conclusion that Warthin's tumour arises from salivary duct inclusions within intra parotid lymph nodes, in a similar manner to the hypothesis of branchial cysts arising from epithelial inclusions within cervical lymph nodes.[30] However, other work suggests a clonal origin associated with a fusion oncogene transformation.[31]

These tumours typically grow slowly to form soft, painless swellings, usually at the lower pole of the parotid gland. They are not infrequently bilateral. A few may undergo rapid expansion possibly caused by cystic change.

Carcinomatous change in Warthin's tumours has only exceedingly rarely been reported and may, in some cases, be secondary to irradiation. Onder et al. have reported a case of poorly differentiated adenocarcinoma in a Warthin's tumour with severe dysplasia of the oncocytic cells in other areas. They have also summarized the features of 14 previous reports in the English literature. These show that the carcinomas can be adenocarcinomas, squamous cell or undifferentiated.[32] This may not represent malignant transformation as such, but represent dual pathology, or erroneous pathology.

The treatment of Warthin's tumour is generally through surgical excision. FNAC will often be diagnostic or at least suggestive of the diagnosis and most tumours are managed through a partial superficial partotidectomy. However, bearing in mind these tumours may not grow, are not associated with a significant chance of malignant transformation and often occur in the older age group, patients with Warthin's tumours can be managed conservatively with observation only, given a diagnostic FNAC result.[33]

Myoepithelioma

Myoepithelial cells are a prominent component of pleomorphic adenomas. Tumours derived solely from myoepithelial cells are rare. Myoepitheliomas are considered to be variants of pleomorphic adenoma that are characterized by overwhelming myoepithelial proliferation. A carcinomatous variant is also recognized. This tumour has no distinctive clinical characteristics. The average age at presentation is 40 years but both children and the elderly can be affected. There is no apparent predominance in either sex and all salivary glands can be affected. Management is essentially the same for pleomorphic adenomas.

Oncocytoma (oxyphilic adenoma)

Oncocytomas are rare tumours. They are predominantly tumours of those over middle age. Women, usually in the seventh or eighth decade, are more likely to be affected. The parotid glands are by far the most frequent site. These tumours are slow growing and may rarely be bilateral. Oncocytomas are benign and excision is curative. There have been occasional reports of recurrences and this is likely to be due to other nodules of tumour tissue in the gland.[34]

SURGERY

Parotid gland

Removal of the tumour within an appropriate part of the superficial lobe of the parotid gland (partial parotidectomy) is adequate treatment for the majority of tumours. Those extending into the deep lobe demand a total conservative parotidectomy, although small tumours of the deep lobe may not necessitate removal of the entire superficial lobe (but there is potential concern regarding first bite syndrome – see 'Cervico-parotid approach' below). There is growing evidence in support of extracapsular dissection, yet it still remains a minority practice for parotid tumours.[33]

INFORMED CONSENT AND MANAGEMENT OF COMPLICATIONS

Prior to superficial or total conservative parotidectomy the patient should be warned about the following serious or frequent complications.

Facial weakness

The risk of temporary or permanent facial weakness must be carefully explained as it has a very significant impact on quality of life. The risk of facial nerve damage is related to the extent of the disease, the type of resection and the experience of the surgeon. Neuropraxia usually recovers within 4–6 weeks. More severe injuries cause some degree of degeneration and recovery may never be complete and take 6–12 months or even longer to take place. The risk of permanent facial palsy is in the region of 1–2%.[20] There is a lack of clear data regarding more detail on facial nerve outcomes after parotid surgery, with grading data for example.

Sensory loss

A degree of sensory loss in the distribution of the greater auricular nerve, over the angle of the mandible and inferior two-thirds of the pinna, is unavoidable. Most patients learn to accept this deficit and few are severely troubled by it. The area of sensory loss generally decreases in the first 12 months post-operatively. If the posterior branch of the greater auricular nerve can be preserved at surgery, there may be less reduction of sensation, both long term and short term.

Cosmetic defects

The cosmetic appearance of the incision rarely causes huge concern, because the most visible components of a Blair's incision (if used) are in skin crease lines. Loss of bulk behind the ramus of the mandible may be visible, more so in thinner patients. This can be mitigated with fat transfer.

Frey's syndrome

Gustatory sweating or flushing (Frey's syndrome) is a socially embarrassing complication of parotidectomy (see **Figure 9.9**). Although it is a problem only in a minority of patients, nearly all patients have some evidence of it if tested with Minor's starch iodine test. The frequency of this complication is sufficient to warrant pre-operative explanation together with the reassurance that it is rarely significantly disconcerting. When it does emerge as a problem, simple preventive measures such as the application of

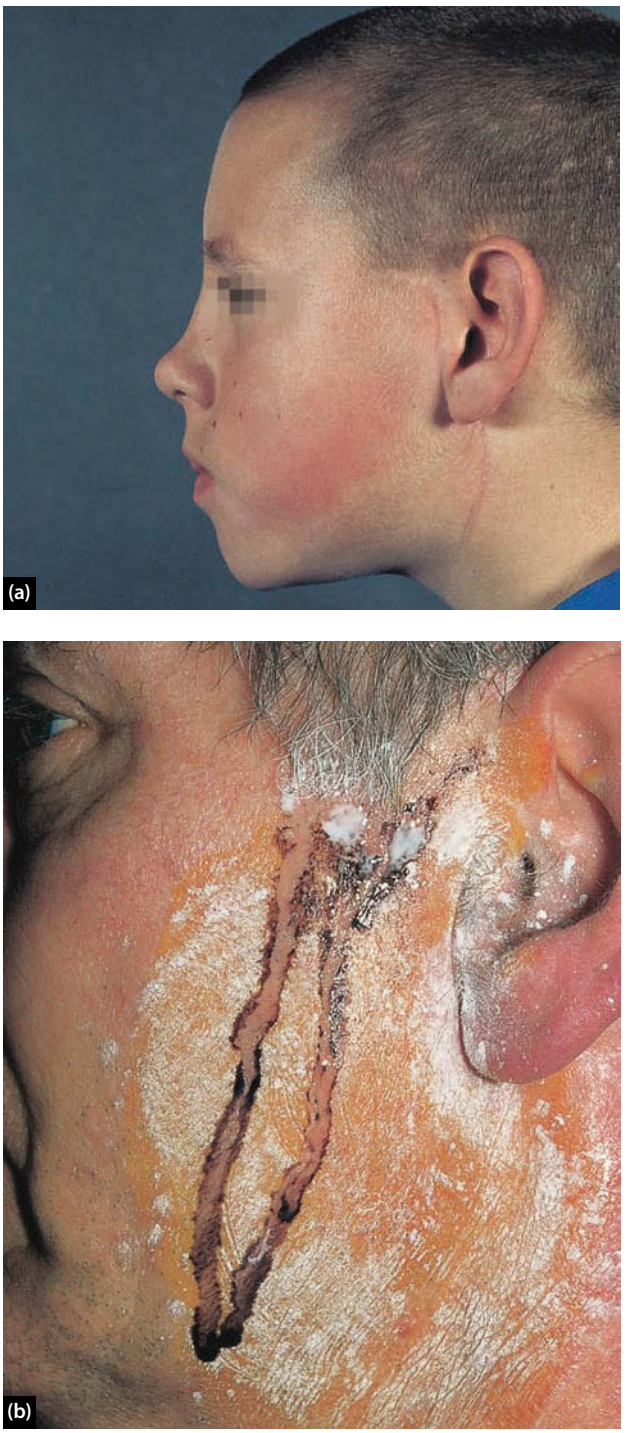


Figure 9.9 Frey's syndrome. **(a)** Classical facial blush elicited by eating flavoured crisps; **(b)** gustatory sweating demonstrated by painting the side of the face with iodine. After this had dried the face was dusted with starch powder. As soon as salivation was stimulated, sweating caused the characteristic starch-iodine reaction.

an anti-perspirant can be used. Otherwise, the standard of care is subdermal injections of botulinum toxin. These need to be repeated at 6–12 monthly intervals.

The risk of Frey's syndrome is decreased by more conservative surgery and the restoration of integrity of the superficial muscular aponeurotic system (SMAS) layer. The use of interpositional flaps (e.g. sternomastoid) can be effective, although the frequency of this complication as a major issue probably does not warrant this as a matter of routine.

Salivary fistula or collection (sialocoele)

Except in total parotidectomy, there will always be a cut surface of the parotid gland from which saliva will leak. This saliva can form a collection (sialocoele) (**Figure 9.10**) or leak through the incision (fistula). When this occurs, it tends to occur within a few days of the surgery. A collection can be quite tense and painful, especially when eating. Collections are aspirated in clinic and this may need to be repeated on several occasions. A leak will need appropriate dressing and maintenance of wound hygiene. Antibiotics should be considered to prevent or treat secondary infection that can occur. Both leaks and collections almost always settle, but it can take 1–2 weeks. Quite why salivary fistulas are not more common is unknown. It could be speculated that those with a significant volume of residual gland, perhaps with an extensive cut surface are more prone to the complication. If there has been ligation of the duct, then it will always happen. Hyoscine patches can be used to reduce saliva production. The next line of treatment when the fistula does not settle conservatively is to inject Botulinum toxin into the main/residual parotid gland (under ultrasound control) and this essentially stops saliva production within a few days and reverses with time (2–3 months).

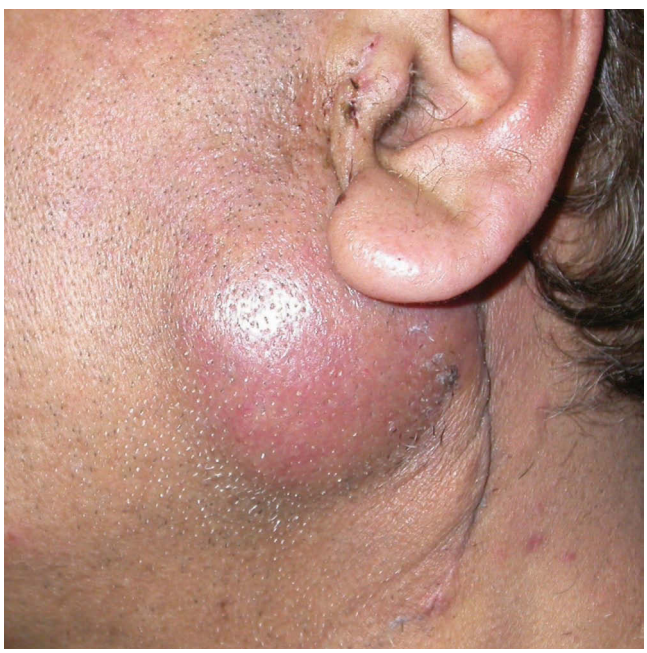


Figure 9.10 Sialocoele after parotid surgery.

Stump neuroma of the greater auricular nerve

When the greater auricular nerve is cut, its end can form a painful neuroma. When this happens, it is often several months/over a year post-operatively. It presents as a very localized tender nodule just anterior to the superior part of the sternomastoid muscle. It can be managed by simple local excision and burying of the fresh nerve end in the muscle. The latter manoeuvre may avoid the complication. If the posterior branch of the nerve is preserved, this may also mitigate against this complication also.

OPERATIVE PROCEDURE

The fundamental principle of superficial parotidectomy is exposure of the facial nerve and then removal of the gland and diseased tissue from around it. The surgeon should be aware that the branching pattern of the facial nerve can be quite varied and that the nerve may have been displaced from its normal position by tumour. Deep lobe tumours may displace the nerve laterally. Identification of the facial nerve and safe manipulation of the tissues around it can be significantly aided by the use of a facial nerve monitor.

Superficial / partial parotidectomy (Figure 9.11)

The patient should not be paralyzed (or at least short-acting agent used only) and be placed in the reverse trendelenberg (head up) position.

Most tumours can be removed through a 'lazy S' (or modified Blair) incision. However in some cases a modified facelift incision is satisfactory and avoids a scar on the anterior (visible) part of the neck. Infiltration of the area with 1:100,000 adrenaline reduces haemorrhage and makes identification of the facial nerve slightly easier. Skin flaps are raised which contain the subcutaneous tissue superficial to the parotid fascia, including SMAS layer. The parotid is then mobilized from the cartilage of the tragal cartilage superiorly and adjacent muscles, the sternocleidomastoid and posterior belly of digastric muscles. It is at this point of the dissection that section of the greater auricular nerve becomes necessary, but preservation of the posterior branch of this nerve should be performed if possible. Wide exposure from superior to inferior, dissecting the gland off the tragal cartilage completely, mastoid tip and sternomastoid with judicious use of traction will aid identification of the facial nerve. When the tumour is around this area, the surgeon should be wary of applying too much traction, as this can cause capsule rupture.

Tragal cartilage, mastoid tip and sternomastoid with judicious use of traction and counter traction will aid identification of the facial nerve.

The facial nerve trunk is then identified. A number of anatomical landmarks facilitate this part of the procedure:

- **The inferior portion of the cartilaginous external auditory canal (tragal pointer)**. The facial nerve lies 1 cm deep and inferior to its tip. The tragal pointer is slightly mobile when retracted so care must be taken when using this as a landmark.

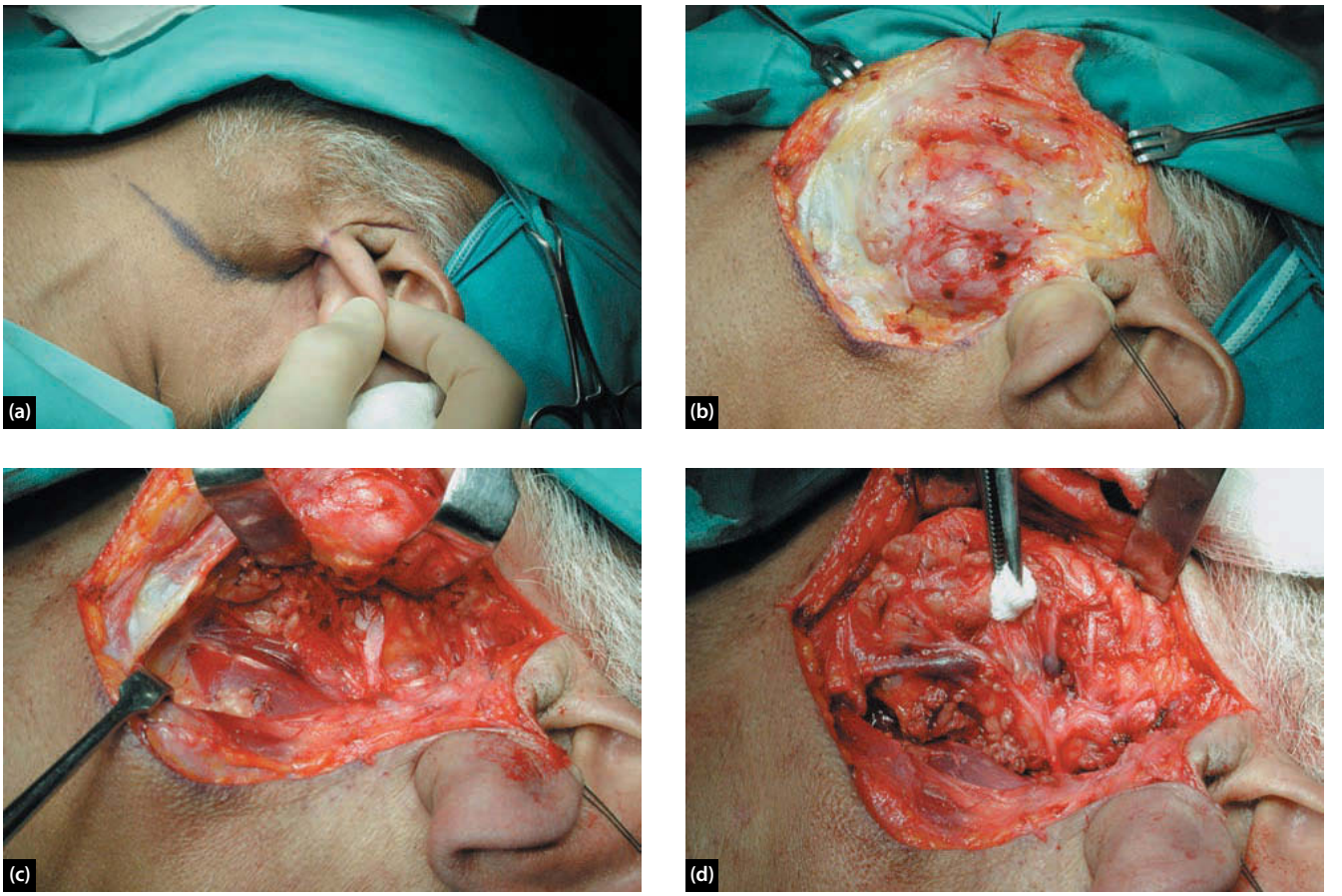


Figure 9.11 Superficial parotidectomy: (a) skin incision; **(b)** identification of posterior branch of greater auricular nerve **(c)** identification of the facial nerve; **(d)** completed dissection.

- **The tympanomastoid suture**. The facial nerve lies immediately deep and inferior to this at its point of exit from the skull. This groove is very easy to feel; and this is an extremely reliable landmark. The surgeon can, literally, get a 'feel' for where the nerve is expected to be.
- **The anterior border of the posterior belly of the digastric muscle**. The facial nerve leaves the skull immediately anterior to the attachment of this muscle. The facial nerve can be exposed by careful dissection in the area immediately anterior to the posterior belly of the digastric in the region of the mastoid process.
- **Care is needed in using the styloid as a landmark**. Whilst easy to palpate it lies deep to the exit of the nerve from the skull so dissection onto the styloid may increase the risk of facial nerve damage.

Rarely, for example in those with large or soft tumours immediately overlying the main trunk of the nerve and in surgery for recurrent disease, it is neither possible nor wise to access the facial nerve trunk at the skull base at the outset of the operation. In these cases it is better to locate and identify one of the major branches and dissect it in a retrograde manner from there. The mandibular branch can be found at the angle of the mandible, as it lies superficial to the facial vessels. The cervical branch of the nerve can be located at the point where it pierces the deep fascia below the body of the mandible. The zygomatic and temporal branches of the upper trunk cross the zygomatic arch anterior to, and within 1–2 cm of, the superficial temporal artery.

In summary, there are a variety of landmarks that can be used to aid identification of the facial nerve and its branches. With experience, the surgeon learns how and when to use this information. Whilst there is no evidence that the routine use of facial nerve monitoring for parotid surgery prevents permanent facial nerve injury[35] and UK practice is variable in this regard, most surgeons would advocate its use in difficult or revision cases.[33] Familiarity with nerve monitoring is therefore essential and it is arguably this, more than any other consideration, that makes a compelling case for its routine use in parotid surgery.

The superficial lobe, or relevant part of the parotid gland and tumour, are then dissected off the divisions and branches of the facial nerve. By this means, the superficial lobe (or part of) is separated from the deeper and other parotid tissue.

In the event of tumour rupture, which, for the reasons explained earlier, can occasionally occur despite good technique, the spillage should be contained and the tissues immediately deep to it removed, including the adjacent aspect of the deep lobe. In this way tissue contamination and seeding is minimized. There is controversy surrounding the traditional teaching of copiously irrigation with

water (not saline) in these situations. That teaching centres on the hypotonic effect on any spilled cells. However, it can also disperse the tumour cells over a wide area.

Haemostasis is then achieved and the wound closed. Drains are usually used, but may not be necessary for lesser resections especially if haemostatic tissue glue is used. Care should be exercised when placing vacuum drains, particularly if there are sections of unsupported facial nerve within the field, as they can be the cause of inadvertent neuropraxia.

Extracapsular dissection (ECD)

The principle of this operation is that the facial nerve is not formally identified. The same incision is made for a standard parotidectomy, and the tumour assessed for suitability for ECD after raising of flaps. Use of the facial nerve monitor is essential. Mobile lesions in the parotid tail are most suitable for ECD, or smaller tumours fairly superficial within the superficial lobe. Inflammatory lesions, large tumours and those extending into the deep lobe are unsuitable for ECD, as are those where malignancy is suspected. An incision is made through the fascia over the lesion and careful bloodless dissection is made down to the region of the tumour. A plane is developed between the capsule of the tumour and normal parotid tissue, with the aid of traction and counter traction from an assistant. The nerve stimulator is used prior to dividing tissue. Care should be taken if retraction distorts normal anatomy, for example if the nerve is inadvertently pulled laterally putting it at risk of damage. If there is doubt about the position of the nerve conversion to a partial parotidectomy with formal nerve identification should be undertaken.

Total conservative parotidectomy (Figure 9.12)

It may be necessary to remove the deep lobe of the gland when either tumour has developed within it or extends into it. Spillage of tumour during superficial parotidectomy is another indication for local resection of the deep lobe. In the latter case, segments of parotid tissue deep to and in between the branches of the facial nerve must be removed and this can be achieved in a piecemeal fashion.

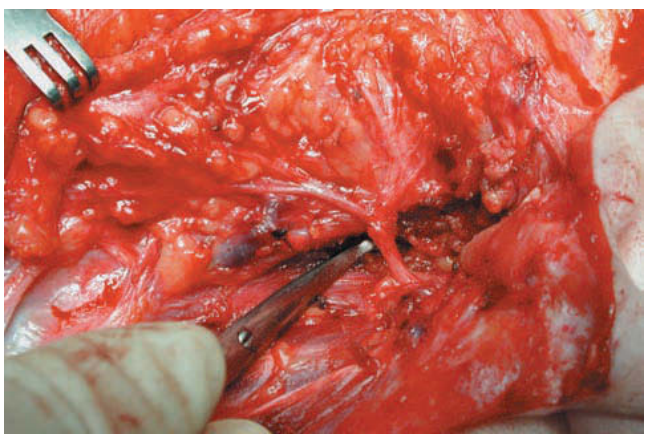


Figure 9.12 Total conservative parotidectomy: the entire gland both superficial and deep to the facial nerve has been removed.

In the case of a deep lobe tumour, usually a superficial parotidectomy is performed. This can be restricted to the inferior. The facial nerve must be mobilized with care. A plane deep to the main trunk is developed followed by more peripheral mobilization. The tumour is removed with all remaining parotid tissue, although this is scant and loose. Hence, the resection generally amounts to an extracapsular dissection.

Cervico-parotid approach to parapharyngeal space adenomas (Figure 9.13)

A complete superficial parotidectomy is not generally required. The lobe portion inferior the main facial nerve trunk and lowest main branches needs to be removed. The facial nerve can then be partly mobilized superiorly. The deep lobe is then removed (unless it is contains part of the tumour (e.g. a dumbbell tumour), in which case it is part of the resection. Access to the parapharyngeal space is then easily established, involving division of the posterior belly of digastric and all of the muscles/ligaments that attach to the styloid process. This should be done accurately, being mindful of the nearby glossopharyngeal nerve. If the process is long, gentle fracture of it can help with access. These manoeuvres allow the ramus of the mandible to be retracted anteriorly, opening up access to the parapharyngeal space.

First bite syndrome

A number of patients develop "first bite syndrome". This is intense pain in the parotid gland when just about to eat and it quickly passes after beginning to eat. There is little published literature on the subject. It probably occurs as a result of sympathetic dennervation of remaining parotid tissue. In the author's experience, treatment with botulinum toxin into the parotid gland can be effective as can high dose gabapentin or Pregabalin. However, this syndrome can be quite debilitating although patients can be reassured that it is generally self-limiting. There is a theoretical argument for performing total parotidectomy at the time of the cervico-parotid approach in order to avoid it, but this would be at the expense of cosmesis and salivary gland function.

Transmandibulotomy/transpharyngeal approach (Figure 9.14)

This is rarely needed. The cervico-parotid approach will facilitate excision of most parapharyngeal space adenomas and this can be combined with transoral robotic access if necessary.

The essential operative steps are as follows:

- Incision – skin crease with lip split. This can be curved alongside the mental skin crease, straight, or angled – all have their advocates.
- Dissection deep and under submandibular gland onto digastric/hyoglossus muscles.
- Identification of hypoglossal nerve.

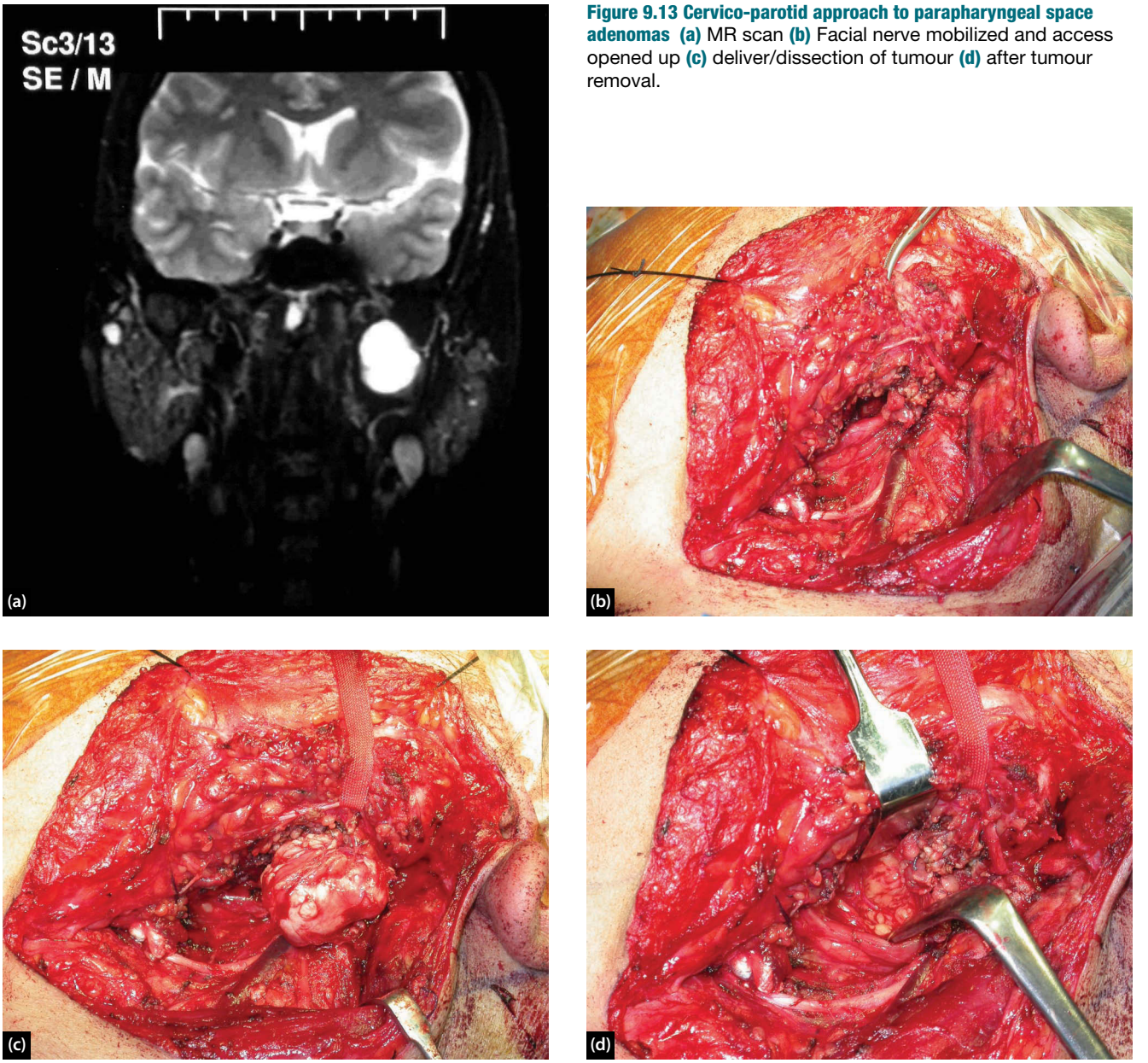


Figure 9.13 Cervico-parotid approach to parapharyngeal space adenomas **(a)** MR scan **(b)** Facial nerve mobilized and access opened up **(c)** deliver/dissection of tumour **(d)** after tumour removal.

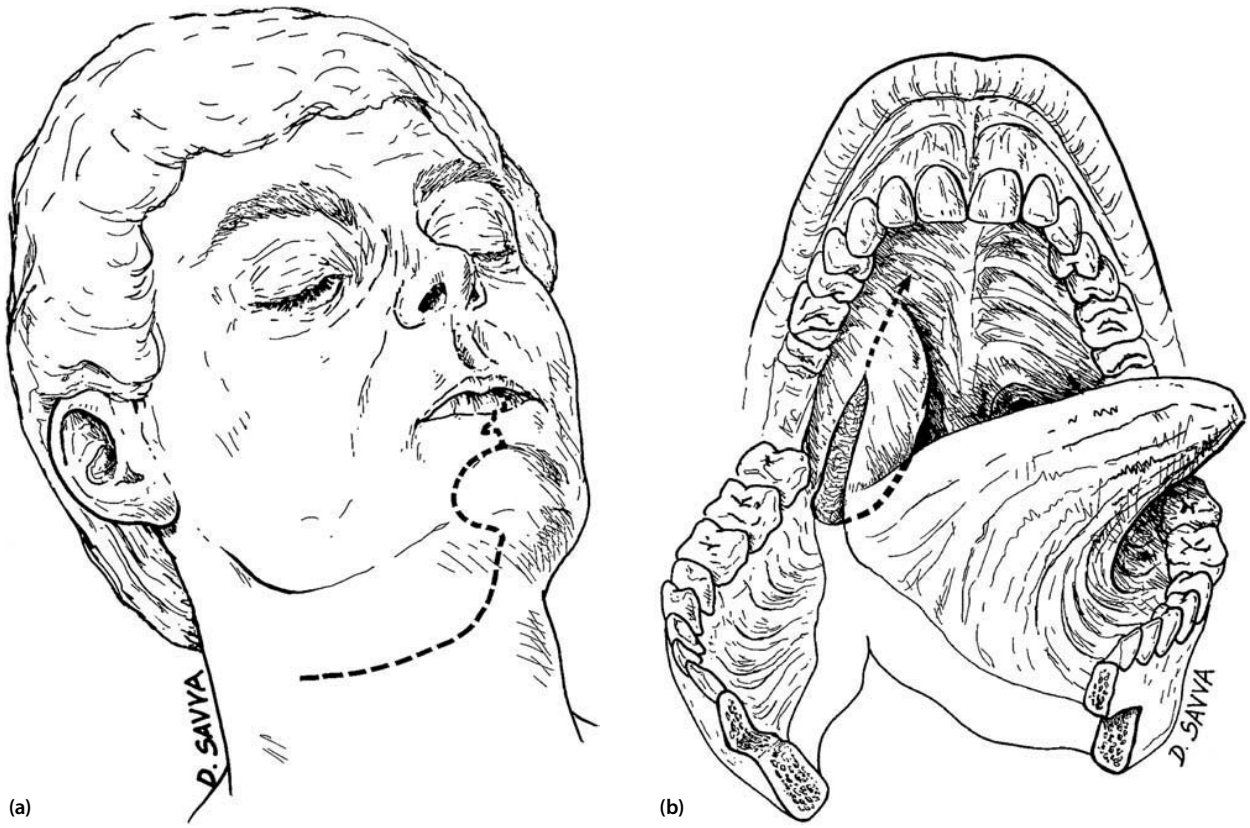
- Paramedian mandibulotomy with pre-plating (2 plates usually). A site between divergent teeth roots can be chosen but sometimes an extraction will be necessary to create the space required).
- The mandible is then retracted laterally so that the incision can be extended between the papillae of the submandibular ducts, along the floor of the mouth and up the anterior faucial pillar to the superior pole of the tonsil. During this part of the exposure the lingual and hypoglossal nerves should be identified and displaced medially, but not overstretched or cut if possible. While it is relatively simple to preserve the hypoglossal nerve, this is not the case with the lingual nerve, which is frequently damaged. Because of this, the patient must be forewarned of the probability of hemilingual anaesthesia following surgery.
- At this stage the exposure is complete and the tumour may be mobilized and removed by blunt dissection. This technique provides excellent exposure of the medial and superior aspects of the tumour which, by any other method, have to be approached blindly. However, caution should be used when dissecting the posterior aspect of the tumour, which is not infrequently adherent to the styloid process/deep parotid lobe. Traction here can cause capsular rupture.

Submandibular gland

Unlike the parotid where only a part of the gland is removed, total resection of the submandibular gland is always indicated for tumours of the submandibular gland.

INFORMED CONSENT

The patient should be warned about the following serious or frequent complications:



(a) (b)

Figure 9.14 Transpharyngeal approach to deep lobe tumours: (a) outline of skin incision; **(b)** osteotomy and opening of floor of mouth and parapharyngeal space. Figures drawn by Despina Savva.

- **Damage to the marginal branch of the facial nerve.** This may result in either a temporary or permanent weakness of the angle of the mouth that will be most noticeable on smiling and puckering the lips. The incidence of this as a permanent complication is around 2–3%.[36]
- **Lingual and hypoglossal nerve damage.** Neuropraxia of the lingual and hypoglossal nerves is unusual but possible. It is more likely to be sustained when the gland is removed for chronic sialadenitis rather than tumour as, in these cases, the gland is likely to be densely tethered to adjacent structures that become more difficult to identify and preserve. This complication is a common source of litigation and so must be included in the consent process. Motor dysfunction of the tongue initially impairs articulation and mastication but the patient rapidly compensates. Ultimately, the tongue muscles waste on that side but without further symptomatic deterioration. The incidence of these complications should be significantly less than 1%.
- **Cosmetic defects.** The patient should be reassured that a properly placed skin incision is unlikely to leave a cosmetically unsightly scar, but that this remains a possible outcome in any patient.[3]

OPERATIVE PROCEDURE

The incision is made in or parallel to a natural skin crease approximately 2.5 cm below the lower border of the mandible and extending for approximately 10 cm anterior to sternomastoid muscle (**Figure 9.15**). It is deepened through the platysma muscle and flaps developed in the fascial plane immediately beneath it. Care must be taken in development of the superior flap as the marginal mandibular branch of the facial nerve runs in the same tissue plane. This nerve enters the neck 1 cm in front of the angle of the mandible, loops over the facial artery and vein 2 cm below the lower border of the body of the mandible before sweeping superiorly to the angle of the mouth. The mandibular branch of the facial nerve can be protected from inadvertent damage by one of two manoeuvres. The facial vessels can be transected at a low level on the surface of the submandibular gland and reflected superiorly. The nerve, which lies lateral to the facial vessels, can then be lifted out of the operative field by traction on the transected end of the vessels. Alternatively, the capsule of the gland can be opened at the level of the hyoid bone and dissection continued beneath it. The elevated capsule protects the nerve in a similar fashion to the first technique. Occasionally, it is very difficult to identify the mandibular branch, and in these cases a nerve stimulator or monitor is extremely helpful.

The superficial part of the gland is mobilized by either blunt or sharp dissection and retracted posteriorly in order to expose the deep portion that lies on the hyoglossus muscle and is partly covered by the mylohyoid muscle. Retraction of the mylohyoid anteriorly, together with posterolateral traction on the gland, brings the lingual nerve, duct and more proximal part of the facial

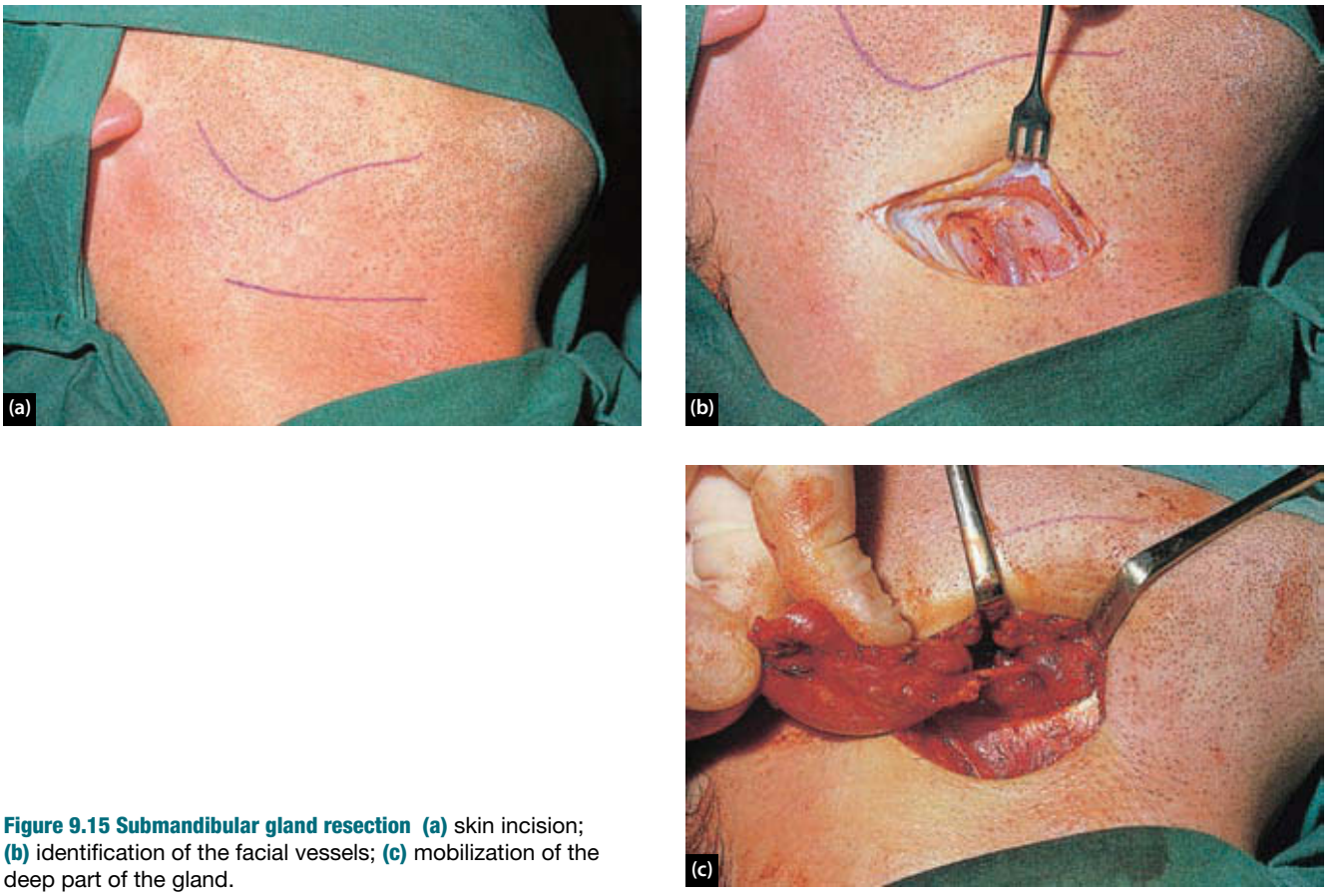


Figure 9.15 Submandibular gland resection **(a)** skin incision; **(b)** identification of the facial vessels; **(c)** mobilization of the deep part of the gland.

artery into the operative field. The lingual nerve appears as a ribbon-like band loosely attached to the body of the gland by a few fibres – the parasympathetic secretomotor supply. Section of these fibres releases the nerve from the gland and permits it to assume a more superior relation. At this stage the hypoglossal nerve may be seen inferior and parallel to the lingual nerve but is sometimes partially covered by the posterior belly of the digastric muscle. The proximal part of the facial artery is usually ligated at this point. The gland is then further mobilized from the hyoglossus muscle about its duct so that this may be ligated and transected as far anterior as possible. A small vacuum drain is inserted and brought out through the skin posteriorly. The wound is closed in two layers.

POST-OPERATIVE FOLLOW-UP

Long-term follow-up for all cases with surgically treated benign disease is unnecessary.[18] For pleomorphic adenoma, the chance of local recurrence is small; when it does occur, the median to recurrence is around a decade; and it is the patient who usually detects the recurrence.

Patients in whom long-term follow-up is advisable include those with:

- incomplete resection (as distinct from completely excised but with incomplete capsule)
- tumour rupture/spillage at operation
- complications that need management
- recurrent disease.

BEST CLINICAL PRACTICE

- ✓ A retromandibular fossa or cheek mass should be considered a salivary gland tumour until proven otherwise.
- ✓ Undertake fine-needle aspiration biopsy on all suspected salivary gland tumours, preferably under ultrasound guidance.
- ✓ Image all deep lobe tumours, those in which malignancy is suspected, congenital tumours and those patients with recurrent disease.
- ✓ Undertake an appropriate parotidectomy every time and never an enucleation.
- ✓ Use facial nerve monitoring in parotid surgery.

FUTURE RESEARCH

- ➤ There is a lack of multi-institutional prospective outcome data for benign parotid surgery.

KEY POINTS

- The incidence of salivary gland tumours is around 6–7 / 100 000 / year.
- Most of these develop in the parotid gland and are pleomorphic adenomas.
- Around 75% of salivary gland tumours are benign.
- The chance of malignancy is higher in submandibular gland and minor salivary gland tumours.
- Most benign salivary gland tumours present in an insidious fashion, growing slowly over a long period of time with little else in the way of symptoms.
- Imaging is performed in most patients. Ultrasound is the primary and initial imaging modality for benign tumours. Cross-sectional imaging should also be performed for larger tumours and complicated cases, such as suspected deep lobe extension or malignancy.
- Fine-needle aspiration biopsy should be undertaken in all salivary tumours, preferably under ultrasound control. Tru-cut biopsy is an alternative, but is usually reserved as a second line investigation.
- The degree of encapsulation of pleomorphic adenomas varies between and within tumours. Areas of deficient or complete absence of capsule are common and this predisposes these patients to recurrence.
- Some pleomorphic adenomas are extensively mucinous and consequently soft and fragile. These rupture easily if not handled with care.
- Recurrence of pleomorphic adenomas may develop many years (typically around one decade) after primary surgery and occurs in around 2% overall according to most data.
- The incidence of malignant change is low in primary disease (around 1/1000) but greater in recurrent disease (around 3%).
- Synchronous or metachronous tumours are more frequently associated with Warthin's tumours than any other salivary tumour.
- Parotid tumours can be managed by an appropriate parotidectomy (with a safe margin of normal tissue around the tumour where possible and with reference/dissection of the facial nerve) or, when possible, by extracapsular dissection (ECD).
- Submandibular gland tumours are managed by total extracapsular gland excision.

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CHAPTER 10

MALIGNANT TUMOURS OF THE SALIVARY GLANDS

Vincent Vander Poorten and Patrick J. Bradley

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SEARCH STRATEGY

The data in this chapter may be updated by a Medline and Pubmed using the following keywords: salivary gland neoplasms, parotid gland, submandibular gland, minor salivary gland, carcinoma, review, management, molecular biology, pathology, surgery, radiotherapy and chemotherapy.

INTRODUCTION

The broad pathological classification of malignant tumours of the salivary gland comprises epithelial tumours, being the most frequently encountered (>80%), mesenchymal tumors which are a very mixed group (<20%), and haematolymphoid tumours (lymphoma and plasmacytoma) making up the remainder of the 2017 WHO classification. Epithelial salivary gland malignancies form one of the most complex diseases in head and neck oncology, due to their low incidence and heterogeneity, both in microscopic appearance and clinical behaviour. A distinction should be made between the paired major salivary glands (parotid, submandibular and sublingual) and the minor salivary glands. The latter are unencapsulated seromucinous glands distributed throughout the entire upper aerodigestive tract, numbering between 500 and 1000, with the majority (<90%) being located in the oral cavity and oropharynx.[1]

INCIDENCE

Epithelial tumours account for the majority (95%) of malignant salivary gland tumours, but are infrequently encountered. Malignant salivary gland tumours are diagnosed in 4 to 135 new patients per million in the population per year, the highest incidence being found in the Inuit community of Greenland and the Canadian Arctic.[1,2] The incidence in the United States of America (USA) is 10 new patients per million per year.[3] For Europeans, the incidence is lower; a Danish population-based study reported a comparable crude incidence of 11 per million per year,[4] with lower incidences reported elsewhere in Europe (with Belgium, the Netherlands, the UK and Finland having about 6–7 new cases per million per year).[5–8] Ethnicity and geographical location presumably account for the observed differences in incidence.[2] Interesting data on the 'population impact' of these cancers were published in the Netherlands in 1995, where 89 new salivary gland carcinomas were diagnosed

that year on a population of 15.5 million inhabitants (Netherlands Interdisciplinary Demographic Institute). When spread across the healthcare sectors, it was estimated that a General Practitioner would see one such patient in 50 years of practice, an Otorhinolaryngologist would see about one or two patients a year, and an average Head and Neck Oncology Centre about ten new patients a year.[6]

As these malignancies occur at different anatomical locations, incidence data are reported by anatomical site. Up to 70% arise in the parotid gland[4–6, 9] and typically 1–3% of all head and neck carcinomas are reported to be parotid carcinomas.[10] The World Standard Population age-adjusted incidence of parotid carcinoma in Belgium in the period 2004–2005 was 6 for men and 4 for women per 10^6 person-years, accounting for 3.9% of Belgian head and neck cancers.[5] Ten to 25% of salivary carcinomas arise in the minor salivary glands.[4, 11] The rest are submandibular carcinomas, with sublingual carcinomas being very rare. An example of the proportion is given by the population-based incidence per 10^6 person-years in the Southern Netherlands of 3.2 parotid carcinomas for men and 1.9 for women, as compared to an incidence of 1.0 for men and 0.4 for women for submandibular and sublingual malignancies.[6]

RISK FACTORS FOR DEVELOPMENT OF SALIVARY NEOPLASMS

The influence of environmental and nutritional factors on incidence has been studied in detail. Follow-up of atomic bomb survivors in Japan and atomic disaster survivors in Chernobyl[12] reveals an increased incidence of both benign (Warthin's tumour and pleomorphic adenoma) and malignant (mucoepidermoid carcinoma) salivary gland tumours.[13] The incidence of Warthin's tumour is doubled and multicentric in smokers.[14] Epstein—Barr Virus (EBV) has been implicated in the genesis of bilateral Warthin's tumours and undifferentiated parotid carcinoma.[15, 16] Cytomegalovirus (CMV) infection may have a tenuous link to the development of mucoepidermoid carcinoma, both in mice and in humans.[17] An inverse relationship exists between a diet rich in polyunsaturated fatty acids and the registration of salivary cancers.[18–23] A Danish study found an increased risk of salivary cancer in workers involved with livestock feed processing, possibly related to naturally occurring mycotoxins produced by *Aspergillus spp.* and are described as one of the most carcinogenic substances known.[24]

KEY POINTS

- The incidence of malignant salivary gland neoplasms in the western world is 7 to 12 per 1,000,000 person-years.
- Salivary malignancy increases with exposure to environmental factors, low-dose ionizing radiation and aflatoxins.
- Smoking of cigarettes is related to development of Warthin's tumours.
- EBV infection may predispose to the development of Warthin's tumour and undifferentiated carcinoma.

HISTOGENETIC THEORIES FOR TUMOURIGENESIS

The normal histology of the salivary gland differs according to their anatomical location (major and minor glands) and consists of different combinations and proportions of the basic components, the acini and the ductal system (**Figure 10.1**). Whereas the major glands have a true excretory ductal system, the minor salivary glands are composed of unencapsulated acini with a short or absent ductal system.[11]

Serous acinus cells predominate in the parotid and the submandibular gland, and form only a minority of acini in the sublingual gland. Mucous acinus cells are the main source of saliva in the sublingual and submandibular glands, and are the only source of saliva in minor salivary glands.

The duct system consists of, in increasing diameter, intercalated ducts, striated ducts and excretory ducts. The luminal cells in the ducts are well-differentiated epithelial cells. Abluminal cells, those not in contact with the lumen, consist of myoepithelial cells that are also found at the abluminal side of the acini, and pluripotent basal cells.[25, 26]

Two theories have been proposed to explain the histogenesis of the complicated appearance of normal salivary gland tissue and the complex 'multicellular' histological appearance of salivary gland tumours. The 'multicellular theory' favours a transformation of the entire

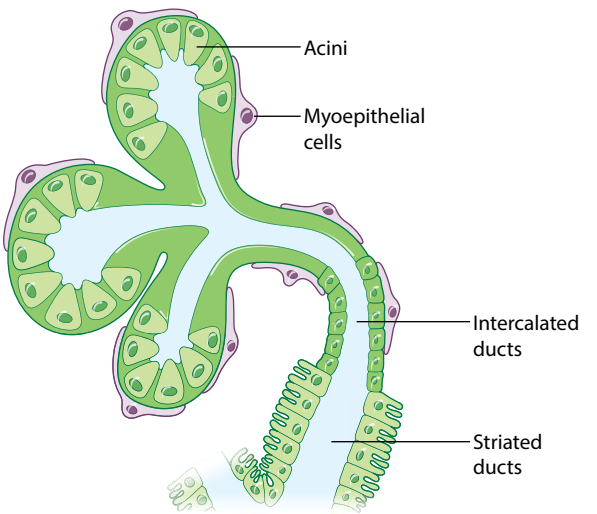

Figure 10.1 Diagram of the normal salivary gland unit. One layer of myoepithelial cells invests the terminal secretory ductoacinar unit – the intercalated duct and the acinus. Source: Tucker AS. Embryology and Clinical Anatomy. *Salivary Gland Disorders and Diseases: Diagnosis and Management*. Bradley PJ, and Guntinas-Lichius, (ed.) Reprinted by permission of Thieme Publishers.

ducto-acinar unit and requires the various 'differentiated' cells to become 'de-differentiated', deranged in their growth pattern, resulting in the microscopically different components observed in the various types of salivary gland tumours.[25] The 'reserve cell theory' states that both the normal salivary gland unit and the different tumour types are the result of differentiation of undifferentiated pluripotent precursor cells, and tumour cells originate from a problem in the normal differentiation process. The earlier in differentiation that a problem occurs, the more undifferentiated and 'high-grade' is the resulting salivary malignancy.

The role of the precursor or 'stem' cell is attributed to the 'epithelial basal ductal cells' that rest on the basement membrane at the abluminal side of the ductal system. Originally, the 'reserve cell theory' was called the 'bicellular' reserve cell theory, distinguishing two types of reserve cells, one at the abluminal side of the intercalated ducts and another at the abluminal side of the excretory ducts.[26–28] The tumours originating from the intercalated duct reserve cells are adenocarcinoma not otherwise specified (ACNOS), acinic cell carcinoma (AcCC), adenoid cystic carcinoma (AdCC), mixed malignant tumour and oncocytic tumours); those said to originate from the excretory duct reserve cells are mucoepidermoid carcinoma (MEC), squamous cell carcinoma (SCC) and salivary duct carcinoma (SDC). The reserve cell theory is supported by recent research indicating the common origin of both the epithelial, myoepithelial and the mesenchymal components of pleomorphic adenoma in exactly these epithelial basal ductal cells.[29]

CLINICAL PRESENTATION AND IMAGING WORKSHOP

The majority of tumours (64–80%) arise in the parotid glands, of which 15–32% are malignant. Seven to 11% arise in the submandibular glands with 41–45% being malignant. Less than 1% occurs in the sublingual gland, where the majority (70–90%) are malignant. Minor salivary gland tumours account for 9–23%, with +/– 80% being malignant.[1, 30]

Parotid gland

The majority of parotid tumours present as asymptomatic, discrete pre-auricular or infra-auricular lumps. With 80–90% of parotid salivary tissue being located lateral to the facial nerve (VIIN), a similar proportion of all neoplasms (benign and malignant) arise in the superficial lobe. A small percentage present only as a swelling of the soft palate or lateral oropharynx,[31] and 1% arise in the accessory parotid gland (along the Stensen duct).[32]

About 1 in 4 parotid tumours are malignant[33] and a diagnosis of a malignancy is suggested by a rapid increase in size, pain, associate cervical lymphadenopathy, fixation of the salivary mass to deep structures or facial skin (**Figure 10.2**), or the presence of VIIN dysfunction.[30] Of patients presenting with parotid cancer, 44% have pain[34]

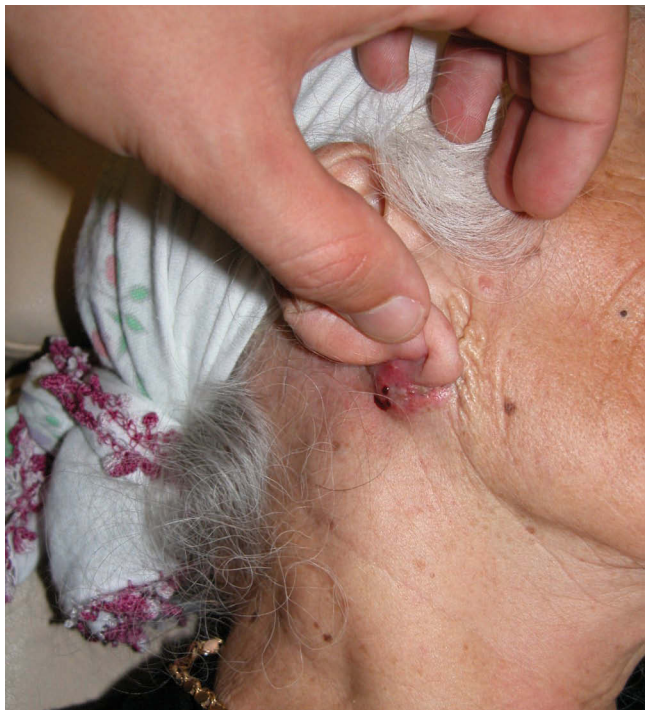

Figure 10.2 Parotid cancer with skin invasion. Source: *Prognosis in Head and Neck Cancer*, Robert J Baatenburg de Jong, editor. V. Vander Poorten: Prognosis in patients with parotid carcinoma; Chapter 21, p 356. Reprinted by permission of Taylor and Francis.

and 25% have VIIN paresis or paralysis which is independent of the tumour size.[30, 34–41] Rarely, the presentation can be insidious. The incidence of parotid carcinoma has been estimated to be as high as 6% in patients presenting with a lower motor neuron VIIN paralysis where no aetiology has been identified after initial MRI scans. This is more likely if the paresis has been slow in onset, progressive in nature, shows no evidence of recovery, affects only isolated branches of the VIIN and if facial tics are present.[42, 43]

The evaluation should include the size, extent, location and the likelihood of the mass being benign or malignant. Imaging is strongly advised when the tumour mobility is impaired, the tumour >4 cm, the VIIN is clinically involved, and there are palpable cervical nodes.[30, 44, 45] Magnetic resonance imaging (MRI) is superior to computerized tomography (CT) in evaluating parotid tumours and allows better demonstration of the retromandibular parotid, the stylomastoid foramen area, VIIN invasion and possible perineural extension.[43, 44, 46] Conventional MRI is complementary to fine-needle aspiration cytology (FNAC) in the pre-operative assessment of a parotid mass.[47] Diffusion weighted MRI (DW-MRI) is considered to have superior diagnostic efficacy in identifying malignancy based on a specific diffusion pattern.[48] Where malignancy is suspected, appropriate imaging should be performed to exclude distant metastases.[49] Positron emission tomography/CT (PET-CT) imaging has high false-positive rates in differentiating benign from malignant salivary disease as common benign tumours (Warthin's tumours and pleomorphic adenomas) demonstrate an increased FDG uptake.[50]

Submandibular gland

Most patients present with a slow-growing, painless mass or swelling under the jaw or occasionally present with distortion of the floor of the mouth, accompanied in exceptional cases by skin invasion or ulceration or even more rarely with local nerve paresis or paralysis. The hypoglossal nerve is most at risk, followed by the trigeminal nerve and then the mandibular branch of the VII nerve. Thirty percent of patients complain of local pain suggesting local tissue extension.[51] Cervical lymphadenopathy is present in 25% of patients. The median symptom duration in the patient group of The Netherlands' Cancer Institute was 13.5 months, ranging from <1 month to >27 years. The median duration of complaints may range from 3 years for low-grade malignancy to 6 months for high-grade malignancy.[52–56] Evaluation of submandibular gland malignancies by radiological imaging is similar to the principles for the parotid gland.

Minor salivary glands (MiSG)

As MiSG are found throughout the entire upper aero digestive tract, the signs and symptoms depend upon the anatomical site involved. The majority of patients diagnosed are in the 5th to 6th decade, but tumours have been documented in children.[11, 56, 57] Fortunately, when diagnosed in children MiSG cancers are low-grade and can frequently be excised with clear margins.[58] Akin to the normal distribution of salivary glands, the most frequent sites of MiSG cancer development are the oral cavity and oropharynx. The most frequent primary site is the hard palate, where MiSG density is highest. The classical presentation is as a painless submucosal swelling, with fixation of the tumour to the overlying mucosa. There may be a small central area of ulceration. Some patients present complaining of their dentures not fitting comfortably as the tumour alters the positioning of the dentures (**Figure 10.3**). When MiSG tumours present in the nose and pharynx, most patients present with obstructive symptoms. Pain or paraesthesia as a complaint has been recorded in >26% of patients[11, 59] and, when present, MRI is required to evaluate named nerve invasion.[60, 61] The presence of regional metastasis is reported in 1 out of every 6 patients.[11, 62, 63]

To estimate the anatomical involvement of the disease process aiming to predict the likelihood of surgical management it is mandatory that CT +/– MRI is performed. Recent reports suggest that the T-max (time to maximum contrast enhancement) in contrast to enhanced MRI scanning is helpful in differentiating benign from malignant MiSG tumours.[64] DW-MRI, which is of value for the pre-operative identification of malignancy based on the tissue-specific diffusion pattern of major salivary gland tumours, has not been studied specifically for MiSGC.[48]

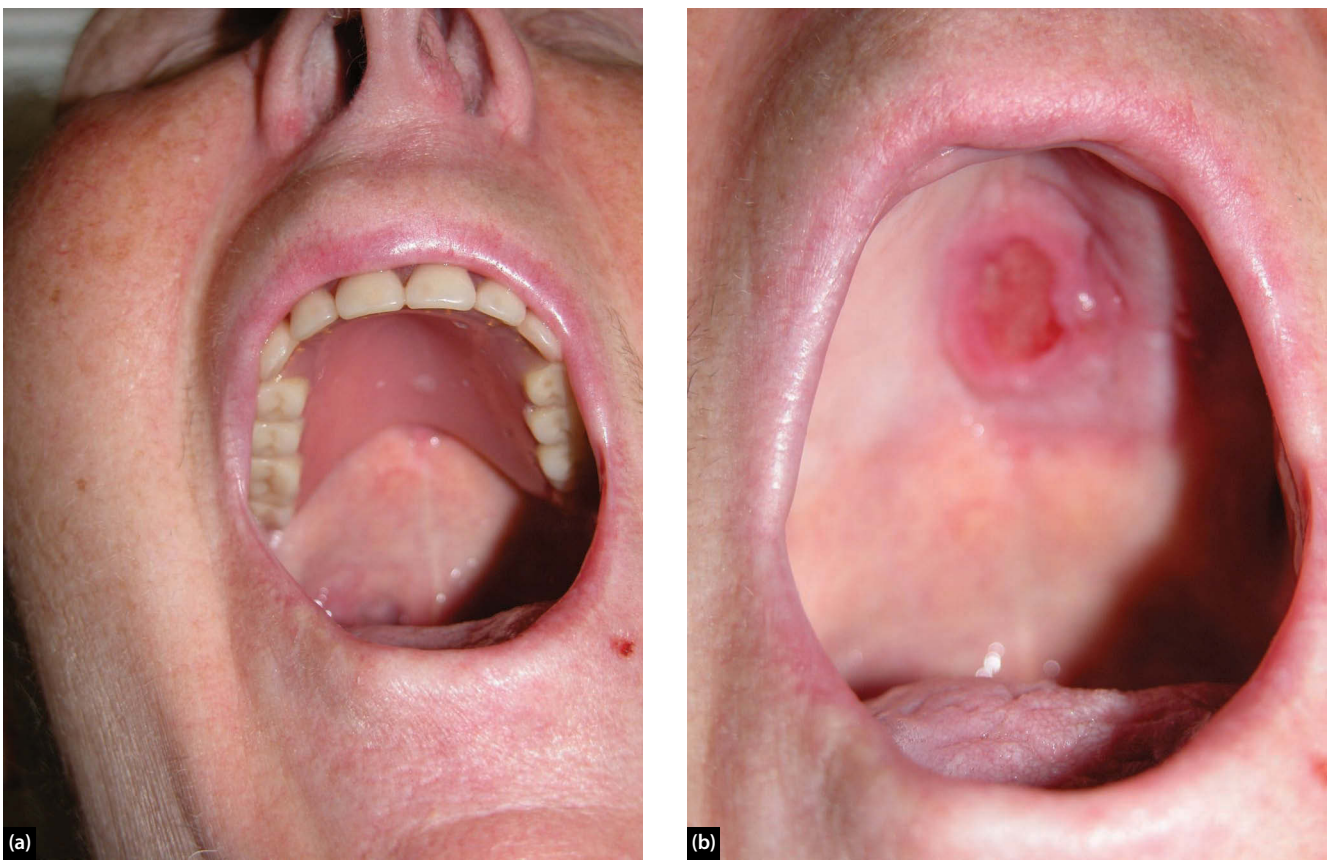

Figure 10.3 (a) and (b) MiSGC of palate with ill-fitting denture. Source: *Squamous cell cancer of the neck*, Robert Hermans (ed). V. Vander Poorten: Epidemiology, pathology and clinical presentation: Chapter 1: p. 15. Reprinted by permission of Cambridge University Press.

It can be questioned however whether this complex imaging will yield any additional information, when, for MiSG tumours, an incisional diagnostic biopsy is necessary and will provide the histological information needed to plan further treatment. As stated above for major salivary gland cancers, PET with or without CT is useful for the exclusion of metastatic disease.[65]

STAGING OF SALIVARY GLAND CANCERS

All patients should be staged as per the TNM system used for major salivary gland cancers following evaluation (**Table 10.1**).[66] Minor salivary gland cancers are staged as per the anatomic site they originate in.[11, 56, 59, 63, 67–69] The use of a uniform classification system, such as the TNM, allows comparison of outcomes following different treatments to similar tumour stages. TNM components also have an independent prognostic role as shown by numerous studies, which help define and refine guidelines for treatment.[10, 37, 41, 70–73] Similar to major salivary gland cancer, the TNM components and stage groupings for MiSG cancers have been found to be the strong prognostic factors,[11, 56, 63, 74–76] and many studies report that TNM overrules the histological grade.[11, 56, 63, 68] Carrillo attributed an additional independent prognostic value to grade for oral and oropharyngeal MiSG cancers, in addition to anatomical extent as reflected in UICC stage.[57, 77]

KEY POINTS

- The smaller the salivary gland, the less frequent a tumour is likely to manifest, but when it does the more likely is the tumour to be malignant.
- Parotid tumours
  - rapid increase in size or volume, the presence of pain, enlarged neck lymph nodes, fixation to deep structures or skin, or VIIN dysfunction should alert a likely diagnosis of malignancy
  - tumour imaging aims to estimate the extent (summarized in the TNM classification), location and probability of malignancy
  - MRI scanning is mandatory to evaluate invasion of the VIIth nerve, fixation to the deep structures, location at the stylomastoid foramen or deep lobe with the use of CT imaging to evaluate suspected bone invasion.
- Submandibular tumours, although frequently symptomless, are often malignant.
- MiSG tumours commonly present at an advanced disease stage and their extent is summarized as per the TNM classification for that anatomic location.

PRE-TREATMENT HISTOPATHOLOGY TYPING

Accurate characterization of the histology of any malignant tumour is a crucial part of the diagnostic workup. This will confirm true salivary origin of the tumour and permit appropriate treatment planning.

TABLE 10.1 8th Edition (2017) UICC TNM classification and stage regrouping for major salivary gland malignancies

T – Primary Tumour	
Tx	Primary tumour cannot be assessed
T0	No evidence of primary tumour
T1	Tumour 2 cm or less, without extraparenchymal extension*
T2	Tumour >2–4 cm, without extraparenchymal extension
T3	Tumour >4–6 cm, and/or extraparenchymal extension
T4a	Tumour invades skin, mandible, ear canal and/or VIIth nerve involvement
T4b	Tumour invades base of skull, and/or pterygoid plates and/or encases carotid artery
N – Regional Lymph Nodes	
N1	Metastasis in a single ipsilateral node, 3 cm or less in greatest dimension, without extranodal extension
N2a	Single ipsilateral node >3–6 cm, without extranodal extension
N2b	Multiple ipsilateral nodes <6 cm
N2c	Bilateral or contalateral nodes <6 cm
N3a	Node(s) >6 cm, without extranodal extension
N3b	Single or multiple nodes, with extranodal extension**
M – Distant Metastasis	
M0	No distant metastasis
M1	Distant metastasis

Stage Grouping			
Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3	N0	M0
	T1, T2, T3	N1	M0
Stage IVa	T4A,	N0, N1, N2M0	
	T1, T2, T3, T4a	N2	M0
Stage IVb	T4B	any N	M0
	Any T	N3	M0
Stage IVc	Any I	any N	M1

* extraparenchymal extension is clinical or macroscopic invasion of soft tissues or nerve, other than those listed under T4a and T4b. Microscopic evidence alone does not constitute extraparenchymal extension for classification purposes. Reproduced with permission.[66]

** The presence of skin involvement or soft tissue invasion with deep fixation/tethering to underlying muscle or adjacent structures or clinical signs of nerve involvement is classified as clinical extra nodal extension. Midline nodes are considered ipsilateral nodes.

Fine-needle aspiration cytology

FNAC is an important tool in the diagnosis of salivary neoplasms. Accurate tumour typing is not to be expected as a routine, but when performed by an experienced cytologist, FNAC is safe, associated with minimal morbidity and is a reasonably accurate way to differentiate between malignant and benign lesions (accuracy 79%).[78–80] This information aids with the prioritization and timing of

treatment, with the planning of the excision and possible reconstruction, and allows for appropriate counselling. Performing FNAC with ultrasound guidance (UgFNAC) not only helps with diagnosis of the primary tumour but also aids with synchronously staging of the neck and is to be recommended.[46] Immediate on-site processing and evaluation of the cellular quality of the aspirate should be provided, and if the aspirate is deemed unsatisfactory the FNAC can be repeated; this results in higher diagnostic accuracy.[44, 81, 82] The real-life performance of this technique can be deduced from a large French series of 1355 salivary gland FNACs which were correlated with subsequent histological assessment, showing an 80.5% true positive rate, 4.6% suspicious lesions, 11.9% false negatives and 3% of uninterpretable samples.[78] Even if the FNAC suggests benign disease, removal of the tumour for further histopathology analysis remains mandatory.[83] Diagnostic accuracy of FNAC could be improved in the future by implementing high throughput techniques such as cDNA microarrays on the aspirate to give a tumour-specific overview of overexpressed oncogenes and underexpressed tumour suppressor genes.[84]

Incision biopsy

For MiSG tumours, FNAC can often correctly classify the tumour as benign or malignant, but may be unable to distinguish between subtypes or provide tumour grading. Whereas incisional biopsy is not recommended for the diagnosis of major salivary gland tumours (except for large tumours with skin ulceration or infiltration), it is appropriate for MiSG locations, where the mucosal tumour is readily accessible for biopsy and will not interfere with subsequent definitive treatment. Excisional biopsy of MiSG tumours has a high rate of positive margins, makes orientation and margin assessment of the definitive resection specimen more difficult and is not to be recommended.

The most important factor in the pre-operative evaluation is to obtain an accurate histopathologic subclassification of the MiSGC (**Table 10.2**) and, when possible, an indication of the tumour grade.[85] The caveat to interpreting these biopsies is that many salivary gland tumour types have overlapping histological features. Without seeing the interface between the tumour and the surrounding normal tissue, invasion cannot be adequately assessed which complicates differentiation between benign and malignant tumours. Similar issues are encountered in interpreting FNAC where less information is to be obtained from individual cells, without the architecture.[86] Some tumours at presentation will be at an advanced stage and the biopsy may be the only tissue sample obtained. Additional histological prognostic features, such as perineural growth (**Figure 10.4**), lymphovascular invasion, and involved margins, can usually only be obtained from a resection specimen. Increasingly, molecular biological studies are performed, and many can be carried out also on the incisional biopsy material.

TABLE 10.2 The WHO* 2017 Histologic Classification of Malignant Salivary Gland Tumours[204]

Type WHO	Abbreviation
1. Mucoepidermoid carcinoma	MEC
2. Adenoid cystic carcinoma	AdCC
3. Acinic cell carcinoma	
4. Polymorphous adenocarcinoma	PAC
5. Clear cell carcinoma	CCC
6. Basal cell adenocarcinoma	BAC
7. Intraductal carcinoma	
8. Adenocarcinoma, NOS	
9. Salivary duct carcinoma	SDC
10. Myoepithelial carcinoma	
11. Epithelial-myoepithelial carcinoma	EMC
12. Carcinoma ex pleomorphic adenoma	
13. Secretory carcinoma	
14. Sebaceous adenocarcinoma	
15. Carcinosarcoma	
16. Undifferentiated carcinoma	
17. Large cell neuroendocrine carcinoma	
18. Small cell neuroendocrine carcinoma	
19. Lymphoepithelial carcinoma	
20. Squamous cell carcinoma	
21. Oncocytic carcinoma	
22. Sialoblastoma (uncertain malignant potential)	

* WHO: World Health Organization. Modified from the WHO publication to include only the malignancies.

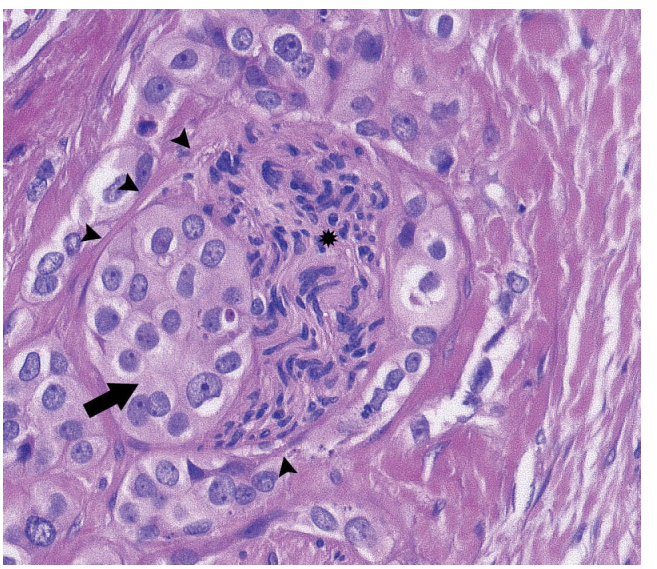

Figure 10.4 Perineural spread of salivary cancer. Arrowhead demarcates perineurium, distended by tumour cells (arrow), compressing the nerve bundles (asterisk). Source: Hermans R. (ed.). *Head and Neck Cancer Imaging*, Vander Poorten V. Epidemiology, risk factors, pathology and natural history of head and neck neoplasms; Chapter 1, p. 13.

Core biopsy

There have been several recent reports discussing the added value of ultrasound-guided core biopsies (UGCB) in salivary gland tumours, with some stating that GCB is so much more accurate than FNAC, that it should become the new standard.[87, 88] There is, however, a theoretical increased risk for complications in the form of tumour seeding (not clearly reported in the literature – but probably strongly underreported) and, especially for parotid tumours, the risk of facial nerve damage (not reported, but in the practice of one of the authors, two patients were documented with VIIth nerve frontal branch damage following UGCB). As these complications are probably poorly reported, and follow-up is frequently too short to know the real effect of tumour seeding, a recent meta-analysis finding no difference between FNAC and USCB, has probably limited bearing.[89] A balanced attitude is probably that, in clinical units where FNAC is quite accurate, USCB can be utilized when FNAC is equivocal or non-diagnostic.[90, 91]

KEY POINTS

- Pre-treatment cytological assessment should be performed for major salivary gland tumours should be performed using FNAC; in selected instances UGCB can be performed, and UGCB or incisional biopsy can be considered when there is associated skin ulceration.
- Incisional or punch-biopsy for MiSG tumours is the standard of care.

SURGICAL TREATMENT

Parotid cancer

PRIMARY SITE

There is strong evidence that primary surgical excision of parotid cancer is the treatment modality providing the best chance of cure.[9, 71, 92] The extent of primary surgery is determined by the size of the lesion, the relationship to the VIIN and extraparotid tissue invasion. The majority of parotid cancers (80%) are located in the superficial or lateral parotid lobe, with a normal functioning VIIN. Performing the standard superficial or lateral parotidectomy would appear to be adequate in the majority of small cancers. Until a prospective randomized evaluation proves the oncological benefit of removing the deep lobe to address occult metastatic disease, to date very little local recurrence has been observed in tumours that are well localized in the superficial lobe and that are adequately removed. It is very likely that the use of post-operative radiotherapy will also aid with the control of possible located microscopic deep lobe lymph node deposits.[93]

Tumours <4 cm, located in the parapharyngeal or deep lobe, or with VIIN involvement should have a more extended surgical procedure, such as a total or radical parotidectomy (**Figure 10.5**). The reasoning for a total parotidectomy is that in locally advanced, high-grade parotid malignant salivary tumours, intraparotid lymph nodes may harbour metastatic disease and be overlooked or not resected should a lesser procedure be performed.[33, 94, 95] Indeed, Armstrong et al. showed that the parotid lymph nodes are involved in 53% of elective neck dissections.[96] Most pre-operatively intact nerves can be dissected macroscopically free from the tumour. VIIN branches are only to be resected when pre-operatively paralyzed or peri-operatively invaded by or surrounded by tumour.[97] More sensitive than clinical examination is electromyography and this can be performed in suspected malignant tumours to support in counselling the patient on the possible need for nerve resection and reconstruction.[98] There is consensus that microscopic disease left behind on a spared nerve branch can be controlled by the use of post-operative radiotherapy.[38, 71, 83, 97, 99, 100] Nerve sacrifice in these instances often induces disproportionate morbidity at the expense of minor gain in tumour control.[39, 97, 100] When the facial trunk or branch resection has been performed, frozen section of the cut margins is recommended to avoid the possibility of leaving tumour skip metastases. Immediate cable grafting results in optimal functional outcomes. The greater auricular nerve (GAN) combines easy access, good diameter and adequate arborization; [101, 102] for longer defects the same donor nerve can be traced back to include cervical sensory branches. The sural nerve is a good alternative.[98] Electromyographic (EMG) signs of reinnervation appear after 4.5 months, followed by the first movements about the 6th month. It can be up to 2 years before the final function is realized, usually a House-Brackman grade III to IV.[98, 101, 102] Factors that negatively impact on the final result of nerve grafting include age >60 years and the presence and duration of the pre-operative VIIN dysfunction.[98] Radiotherapy does not impair the final results of cable grafting: Brown et al. reported a House-Brackmann grade III or IV in 69% of irradiated patients versus 78% of non-irradiated patients (p = 0.54), and replicated previous reported experimental findings of 80% axon recovery in both irradiated and non-irradiated facial nerves.[102, 103]

NECK DISEASE

N+ neck

Parotid cancer related cN+ disease requires a comprehensive (modified radical) neck dissection, removing levels I to V.[104] Where appropriate, based on invasion or proximity to the metastatic disease, the non-lymphatic structures (nerve XI, jugular vein or sternocleidomastoid muscle) may need to be sacrificed.[105] Recent studies corroborated this 'old knowledge': pN+ involvement in a recent study from the Memorial Sloan Kettering Cancer Center reached 52% in level I, 77% in level II, 73% in level III, 53% in level IV and 40% in level V.[106] Also a comparable Korean study reported pN+ rates of 43% in level I, 90% in level II, 40% in level III, 57% in level IV and still 43% in level V.[107] In pN+ patients, post-operative adjuvant radiotherapy to the parotid and the ipsilateral neck doubles locoregional control and improves survival.[73, 105, 108–110]

N0 neck

In patients with a cN0 neck at presentation, performing an elective neck surgery depends on the presence of the

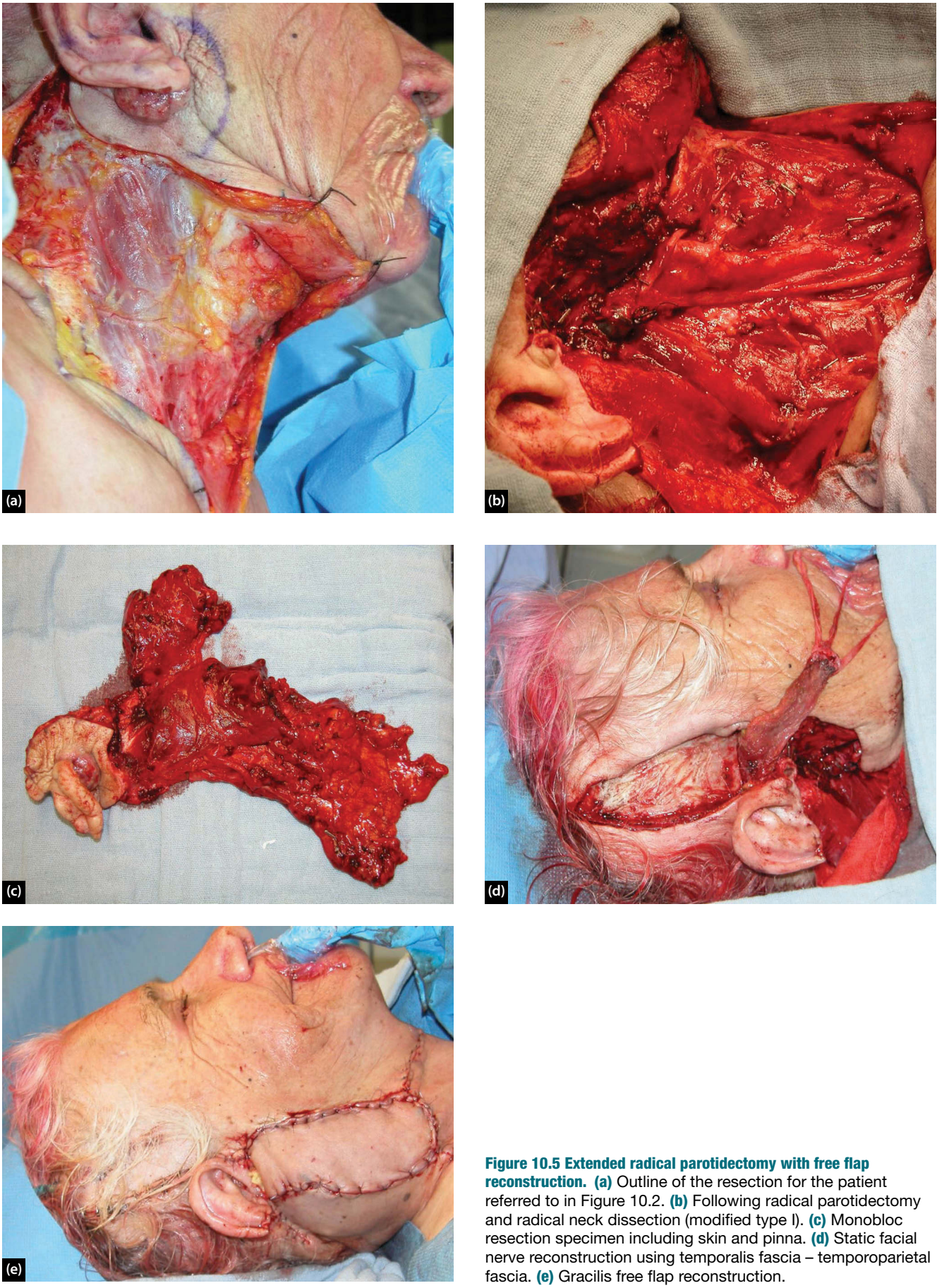

Figure 10.5 Extended radical parotidectomy with free flap reconstruction. **(a)** Outline of the resection for the patient referred to in Figure 10.2. **(b)** Following radical parotidectomy and radical neck dissection (modified type I). **(c)** Monobloc resection specimen including skin and pinna. **(d)** Static facial nerve reconstruction using temporalis fascia – temporoparietal fascia. **(e)** Gracilis free flap reconstruction.

risk factors for occult neck disease, but the alternative of using elective radiotherapy is also shown to be effective in controlling neck disease.[109] The authors routinely perform frozen section of level II nodes at the commencement of the procedure and if these contain macrometastases, we consider the neck as cN+ and proceed with a neck dissection.[41, 80, 83, 92] The recognized risk factors for the presence of occult neck disease are tumour size >4 cm and histology with clinical high-grade behaviour, implying a 20% and 49% risk for occult nodal metastasis respectively.[96, 109, 111] Age >54, perilymphatic spread and extraparotid extension, together correspond to a 95% risk.[111] These high-risk patients require elective neck treatment, be it neck dissection or radiotherapy. Parotid AdCC rarely causes lymph node metastasis, so an elective neck dissection is not really indicated in this high-grade malignancy.[92]

Some authors propose a routine elective neck dissection of for all parotid carcinoma patients; using this strategy Zbären finds a 22% occult rate and a better 5-year locoregional control as compared to that of 'an observation policy', but the patients in this series did not receive radiotherapy.[112, 113] Stennert reports even a 45% occult rate in a large series of patients all of whom underwent neck dissection.[33] A Brazilian study reported a 37% occult metastases rate predicted by T-classification, severe desmoplasia and histology (adenocarcinoma, undifferentiated carcinoma, high-grade MEC, SDC and SCC, together resulting in a 68% occult rate).[114] The surgical approach to the N0 neck can be fine-tuned using pre-operative USgFNAC of the neck and the use of peri-operative frozen section.

The MD Anderson strategy is elective radiotherapy to the N0 neck in high-risk patients, relying on definitive histopathology of the resected primary; this is appealing because the indications for elective neck treatment concur with the indications for post-operative radiotherapy to the primary, and also because pre- and peri-operative typing of salivary carcinomas is very difficult (accuracy 51–62%).[111, 115] This means that the information required to pre-operatively classify a parotid tumour as high risk is often not available during elective surgery and at the time of decision to perform a neck surgery.[44, 105, 115] Furthermore, radiotherapy may still be indicated if a cN0 neck turns out to be pN+.[93, 110] Only conducting a prospective randomized trial will answer the question whether an elective neck dissection (followed by radiotherapy if indicated) provides a better result than elective radiation alone to the cN0 neck.

Submandibular gland cancer

The standard treatment in the last decades has shifted from a rather aggressive and extended surgery as monotherapy[52, 63, 107, 116] to more limited and functional surgery, tailored to the local pathological involved anatomy, supplemented by post-operative radiotherapy.[53–55, 71, 117, 118] The typical standard operation included the submandibular gland in a radical neck dissection, often with *en bloc* excision of the floor of mouth and lower rim of the mandible.[52, 116] The move over time toward conservation surgery was illustrated by Spiro et al.,[71] who described the use of level I-II-III neck dissection for none of the patients in the period 1939–1965 to 38% of the surgeries in the study period 1966–1982. In the Netherlands' Cancer Institute, the level I-II-III dissection comprising the submandibular gland was used, in the cN0 neck and absence of invasion of bone or floor of mouth, and accounted for 66% of operative procedures in the period 1973–1983 and for 71% of the procedures between 1984 and 1994.[55] The current agreement is that for early stage, low-grade disease, the minimal procedure that should be performed, should be complete excision of the gland within a levels Ia and Ib lymph node dissection. For most other disease that is further cN0, a level I-II-III elective dissection encompassing the submandibular gland is the recommended extent of surgery. This operation should only be extended beyond the boundaries of the supraomohyoid dissection, if the local extension of the disease dictates so.[53] Commonly there is cN+ disease, and then a comprehensive neck dissection is mandated.[119]

Sublingual gland cancer

AdCC is the most common malignant tumour of the sublingual gland (72%), followed by MEC, however other SGC have also been reported, usually as case reports. The initial treatment should be surgery, performed after confirmation of histology and imaging, to encompass the extent of the primary tumour. Tumours <2 cm in size and mobile may be resected intraorally but it is also recommended that the ipsilateral submandibular gland or level I be removed, as the submandibular duct is likely to be resected. Tumours >2 cm should receive an *en-bloc* resection, possibly using a 'pull through' procedure or a mandibulotomy approach. Performing an elective neck dissection (levels I–IIa) may facilitate such a surgical procedure in the N0 situation. In the N+ neck, a therapeutic neck dissection such as a modified radical neck dissection should be performed. Adjuvant post-operative radiotherapy is indicated for patients with advanced stage disease (stage III/IV, high-grade tumours, perineural involvement, positive surgical margins, >2 N+ lymph nodes and/or pathological evidence of extracapsular extension.[120]

KEY POINTS

- The preferred treatment of parotid and submandibular gland cancer treatment is surgery.
- VIIN-preserving parotidectomy (allowing for microscopic remnant disease if unavoidable – followed by radiotherapy) in a patient with a pre-operatively functioning VIIN is considered the standard of care.
- Gross tumour involvement of the VIIN requires nerve resection followed by immediate cable grafting.
- The N+ neck requires surgery, the N0 neck should be treated electively surgically or by radiotherapy, depending on the risk factors.
- Post-operative radiotherapy improves locoregional control depending on the prognostic factors present.
- For submandibular gland malignancy, the minimally required surgery is a gland resection within a level I-II-III neck dissection (selective neck dissection); the indication for post-operative radiotherapy follows that for parotid gland malignancy.

Minor salivary gland cancer (MiSGC)

GENERAL CONSIDERATIONS

The primary

The treatment of choice for MiSGC is wide local resection with tumour-free margins. Resectability is determined pre-operatively, based on clinical and imaging findings, the anatomical site of origin, the histology and the available surgical expertise. These factors also determine the extent of resection necessary and the functional implications of a resection. In all reported series, resection margin status is one of the most important survival outcome prognostic factors that correlate strongly with both anatomical extent and histological type.[11, 121, 122]

The neck

Currently, surgical treatment of the neck is only indicated when 1) there is clinical or radiological evidence of regional metastasis (N+), or when 2) the risk of subclinical disease in a clinically negative neck exceeds 15–20% and when 3) the neck is surgically entered as an approach to the primary.

Clinical N+ disease occurs in about 15% of patients.[11, 123] Except in patients with high-grade cancers such as high-grade mucoepidermoid carcinoma, the occult metastasis rate is too low to justify elective surgical treatment.[124, 125] Nasopharyngeal salivary cancers are also an exception, where a high rate of occult disease has been reported following elective neck dissection in a series of patients amenable to surgery.[126] For patients with pN+ disease, post-operative radiotherapy improves locoregional control and survival.[73, 110]

SITE-SPECIFIC CONSIDERATIONS[122]

Oral cavity

The most common subsites are the palate, buccal mucosa, retromolar trigone and upper lip, accounting for +/– 75% of cases. The palate is the most common site (55%) with +/– 60% of these being malignant. In a series from the Netherlands' Cancer Institute, 78% of minor salivary gland cancers were located in the oral cavity.[11] In 149 patients with palatal MSGT seen over a 46-year period at the MD Anderson Cancer Center, malignant tumours were found in 116 patients (78%), with 50% of these tumours on the hard and the other 50% on the soft palate.

The majority (up to 90%) of the oral cavity MiSGC are MEC, AdCC and PAC.[122, 127] Akin to the growth pattern, patients with MEC tend to have localized space-occupying lesions, which present at an earlier stage compared to patients with AdCC, which display an infiltrative submucosal and perineural growth and are at an advanced disease stage when diagnosed. In the MD Anderson series, extensive disease diagnosed locally by radiological imaging showed: local bone invasion 31%, the sinonasal cavities 31%, the sinonasal cavities 31%, the pterygoid muscles 5%, the nasopharynx 3%, and intracranially 3%, but only 3% presented with detectable cervical lymphadenopathy.[75] The latter group need a therapeutic neck dissection in combination with wide excision of the primary. Resection of the primary palatal tumour may require a palatal obturator or free-tissue reconstruction, depending on the size and location of the surgical defect.

Oropharynx

There are few series focusing specifically on the oropharynx, but the tongue base is the most common site of origin. In the Netherlands' Cancer Institute series of patients the posterior tongue was the only oropharyngeal subsite involved.[11] Like in the oral cavity, the most frequent histologies are AdCC and MEC (up to 60%), followed by ACNOS. Treatment – if feasible – is surgery, ranging from transoral laser microsurgery or transoral robotic resections for smaller circumscribed lesions, to suprahyoid release or mandibulotomy and free-flap reconstructions for the larger tumours. Most resected tumours will require post-operative radiotherapy, which is detailed in 'Post-operative radiotherapy' below.

Larynx

MiSGs are found in the submucosa of the subglottis, glottis (floor of the ventricle and the undersurface of the anterior commissure) and supraglottis (especially in the aryepiglottic folds, and petiole of the epiglottis) and account for about 1% of all tumours of the larynx, both benign and malignant. The most frequent laryngeal MiSGC is subglottic AdCC, followed by MEC. Typically, these laryngeal MiSGC are diagnosed at an advanced disease stage when diagnosed, due to their submucosal growth and large size at the time of presentation. The treatment of choice is surgical resection, with endoscopic resection, open partial and total laryngectomy being the options. Post-operative radiotherapy should be considered in all patients especially when unfavourable prognostic factors are present, or in the case of cartilage, perineural or vascular invasion. Laryngeal MiSGC patients frequently develop distant metastasis, usually to the lungs.[128, 129]

Nose, paranasal sinuses and nasopharynx

AdCC is the most frequent MiSGC found in the nasal cavity and paranasal sinuses and due to its advanced stage at presentation results in a worse prognosis than in any other site of the head and neck, implying local recurrences and early perineural and hematogenous spread; around 50% present with distant metastases. Locoregional control is better in those patients receiving more radical primary surgery, with or without post-operative radiotherapy, but there is little data to support radical management over a more conservative approach. Recent progress in surgery, including endoscopic resection, facilitates local surgical radicality and improved surgical reconstruction that allows for timely and optimum post-operative radiotherapy. Use of the gamma knife for residual or recurrent disease optimizes the chances of cure and improves remaining quality of life. A significant number of patients have unresectable

disease at presentation and are treated with primary radiotherapy, explaining why the proportion of MiSGC at this subsite is overrepresented in reported series of AdCC from radiation oncology centres (e.g. 40% in the University of Florida series).[63]

For MiSGC located in the nasopharynx, the most common histology is AdCC (94%), and rarely MEC (6%). AdCC comprised 48% of a large surgical series (n = 23 accumulated during 12 years), MEC 35% and ACNOS 17%. Like MiSGC located in the nose and paranasal sinus, nasopharyngeal MiSGC presents late, typically at an advanced stage of disease with invasion of the skull base, cranial nerve paralysis and intracranial invasion. Complex surgical resections (varying approaches have been described such as lateral infratemporal middle fossa, subfrontal, midfacial degloving, lateral rhinotomy, transoral palatal or maxillary swing approach), possibly transposing or resecting the carotid artery, resection of dura and dissection of cancer from the cavernous sinus, are only possible in a minority of cases. These complex resections demand that expertise for a wide variety of reconstructive options be available, ranging from dural repair using temporalis fascia or a pericranial flap to vascularized flaps. Exceptionally for MiSGC, elective neck dissection reveals occult metastatic disease in about 50% of the patients with tumours in the nasopharynx.[126] Post-operative radiotherapy is always required and will be detailed in 'Postoperative radiotherapy' below. This strategy carries 5- and 10-year disease-specific survival (DSS) rates of 67% and 48% respectively. In non-resectable nasopharyngeal AdCC radical primary external-beam photon radiation seems a good option with a reported local control rate of 45% at 5 years and 5- and 10-year survival rates of 78% and 49%, respectively. Long-term complications may be serious and are less expected with modern IMRT techniques.

KEY POINTS

- The optimum curative treatment for minor salivary gland tumours is surgery.
- The surgical approach and resection should be dictated by the site of origin and can encompass the entire spectrum of head and neck surgical resective and reconstructive procedures.
- Meaningful clear-margin surgery is often impossible to achieve at certain sites because of the extensive local anatomical invasion by tumour at diagnosis (skull base and perineural invasion); in these instances, primary radical radiotherapy may be the first and only choice of treatment available.

RESECTED SPECIMEN: HISTOTYPING, GRADNG AND MOLECULAR STUDIES

Salivary malignancies are categorized as per the 2017 WHO classification (featuring 22 different phenotypes: **Table 10.2**). The characteristics that will also be reported include the tumour grade, and describe negative features such as perineural, vascular and perilymphatic invasion and the margins status. Increasingly, molecular biological markers are being identified and studies suggest that their usage may aid with a more accurate histologic diagnosis and prognosis.[130, 85]

Histologic typing: Light microscopy and immunohistochemistry

The primary histological diagnosis of SGCs is challenging, as can be seen in the 29% reclassification rate resulting from a new histological classification system reported by van der Wal et al.[4, 122, 123, 131] and by a substantial inter-observer variability between pathologists.[60, 132] The Netherlands' Cancer Institute series displayed a 22% reclassification rate.[11] Reclassification, interobserver variability, geographical variation and referral bias all contribute to disparities in the published literature. Only a population-based study can give an accurate idea of the incidence of different histological types.

A clear relationship between histological type and biological behaviour is often lacking, as commented by Spiro[30] and Leivo.[134] In population-based studies, most major SGCs are AcCCs (15–17%), AdCCs (16–27%), and MECs 14.5–19.2%).[8, 40] All 22 malignant salivary tumour types have been described across most sites. In most studies of MiSGCs, AdCC (32–71%) and MEC (15–38%) account for the majority of histological types and far outnumber the other histological variants.[11, 56, 57, 59, 60, 63, 67, 68, 73, 76, 134–137]

The most critical aspect of pathological examination is differentiating these tumours from benign entities, which can demonstrate overlapping histologic features. The proportion of benign to malignant varies across series; those with a higher percentage of malignant disease may suffer from referral bias seen at tertiary centres that are more likely to publish their results.[30, 63, 138]

Grading

Grading is a standard procedure that is performed as a surrogate marker for the biological behaviour within tumours of the same histological type. However, grading suffers from poor inter- and intra-examiner consistency and low independent prognostic power.[11, 56, 131, 132, 139] A clear relationship between histological grade and biological aggressiveness is thus often lacking.[133, 140] In addition, grading often has no therapeutic relevance as most salivary gland cancers are treated similarly with surgery and post-operative radiotherapy, with the exception of completely resected low-grade, low-stage MEC and polymorphous low-grade adenocarcinoma, where post-operative radiotherapy is not required.[44]

Clinical grading combines information from histological type and grade

To facilitate clinical use, the different histological subtypes are divided into low, intermediate and high grades as shown in **Box 10.1**.

BOX 10.1 Grading of salivary gland malignancies based on clinical behaviour

Low:	AcCC, PAC (formerly PLGA), and low-grade MEC
Intermediate:	AdCC and epithelial myoepithelial carcinoma
High:	High-grade MEC, SDC, carcinoma expleomorphic adenoma, ACNOS and undifferentiated carcinoma

When one chooses to work with two groups the intermediate group is clubbed with the high-grade group for the following reasons: AdCC is hard to cure often with a protracted clinical course, and epithelial myoepithelial carcinoma is linked to a recurrence rate of 40% and a DSS of only 60%.[141, 142] It must be noted that this grade assignment does not always parallel clinical behaviour.

Despite these limitations, grading is still an essential part of the workup and decision-making for the three most commonly encountered SGCs: AdCC,[140, 143–145] MEC[132, 139, 146–150] and AcCC.[85, 151, 152] As clinical grading is strongly associated with other consistent prognostic factors such as age[11] and TNM-stage,[56, 140] it is often not retained in the final model in multivariate analysis.

Molecular biology[92, 122, 153]

Protein products of various genes and their corresponding genes in salivary gland cancers have been intensively studied to identify potential prognostic factors and treatment targets.

PROGNOSTIC FACTORS

Cell cycle-based proliferation markers likely represent the endpoint of the accumulation of genetic and epigenetic events that induce deranged growth, reflecting the number of cells going through the cell cycle. The first subject to interest cell biologists in SGC were silver-staining or argyrophylic nucleolar organizer regions (AgNOR); an increased AgNOR cluster to nucleolus volume reflects proliferative activity and correlates with the degree of malignancy. Other intensively studied factors include Ki-67 expression (anti-apoptotic nuclear antigen in proliferating cells), proliferating cell nuclear antigen expression (PCNA, co-factor of DNA polymerase delta), human telomerase reverse transcriptase expression (hTERT) and TUNEL [terminal deoxynucleotidyl transferase (TdT)-mediated dUTP-biotin nick end labelling identifying DNA breaks in apoptotic cells] assays. In SGC, these proliferation markers correlate with optical grading and have prognostic power in AdCC, AcCC, SDC and MEC. Importantly, their contribution is proven by remaining independent factors in multivariate models that include classical clinicopathological factors. The advantage of these proliferation indices is that they are not too expensive, widely applicable, correlate well with prognosis and thus could improve prognostic grouping. In this respect, Ki-67 staining is probably the best studied and most readily available supplementary examination to aid in locating a specific SGC on the scale of biological aggressiveness.

Some of these proliferation markers have also been investigated as therapeutic targets and these are tabulated in **Table 10.3**. What follows is an overview of major advances in SGC molecular biology.

Growth factor receptor proteins and their ligands

Stem cell factor receptor (c-KIT, a transmembrane tyrosine kinase), angiogenesis-related growth factor receptors (VEGFR, PDGFR, bFGFR, IL-8, PlGF , TGFβ), nerve growth factor (NGF), the ErbB/HER family of human epidermal growth factor receptors (EGFR, also named HER-1 through -4 or ErbB-1 through -4), insulin-like growth factors IGF–I/II and receptor IGF-1R, and fibroblast growth factors 1 and 2 and fibroblast growth factor receptor 1 belong to this category. c-KIT is detected in 80–94% of AdCC and in 100% of lymphoepithelial-like SGCs and myoepithelial carcinomas, and in a subset of other tumours as well. In AdCC, the relation between high c-KIT expression (>50%) and grade remains unresolved. In one study this feature was significantly more common in solid type AdCC but Freier et al.[154] found the opposite: high expression only in cribriform and tubular AdCC. As for angiogenesis-related growth factor receptors, Lim et al.[155] describe a prognostic value for vascular endothelial growth factor (VEGF) expression in many SGC. In multivariate analyses, VEGF expression was associated with advanced stage and with worse DSS. EGFR identification and overexpression parallels aggressiveness in MEC, SDC, and AdCC. HER-2 has been found overexpressed in adenocarcinoma, undifferentiated carcinoma, AdCC, SDC and in 30% of MEC. Furthermore, it is a negative prognostic marker in multivariate analysis, independent of histopathological grade, tumour size and regional metastasis. On the other hand, in a recent study, ERBB1/CCND1/PIK3CA co-amplification was the most consistently observed pattern (29%). EGFR amplification correlated with distant metastasis, and the co-amplification pattern translated into a reduced survival. Aggressively behaving AdCC also displays HER-3 expression. Recently increased expression of NGF has been described in AdCC, possibly accounting for its neurotropism. Fibroblast growth factors 1 and 2 and fibroblast growth factor receptor 1 are all overexpressed in salivary gland SGC.

TABLE 10.3 Molecular targets and corresponding therapies studied in salivary gland carcinoma

Molecular target	Salivary gland carcinoma type	Molecular therapy
c-KIT	AdCC	imatinib
ErbB-1	All types	cetuximab gefinitib
ErbB-2	All types	trastuzumab lapatinib
VEGF -family	AcCC	axinitib
NFκB – proteasomes degrading its inhibitor (I-κB)-α	AdCC	bortezomib

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Cell cycle oncogenes

The above-mentioned growth factor-receptor interaction activates cell cycle oncogenes. These include sex-determining region Y-box 4 (SOX-4), nuclear factor κB (NFκB), human rat sarcoma viral oncogene homolog (H-RAS), phosphatidylinositol 3 phosphate kinase/serine-threonine protein kinase Akt (PI3K/AKT), sarcoma (Schmidt-Ruppin A-2) viral oncogene homolog (Src), signal transducer and activator of transcription 3 (STAT3), mammalian target of rapamycin (mTOR, activated by AKT regulates protein synthesis depending on nutrient availability), peroxisome proliferator-activated receptor gamma (PPARgamma), and cyclin D1. In a large microarray analysis of AdCC, Frierson et al. found that SOX-4 was the most significantly overexpressed cell cycle oncogene.[156] Furthermore, increased apoptosis following SOX-4 knockdown suggests that this oncogene exerts its activity via down-regulation of inhibitors of the NFκB pathway (inhibitor protein (I-κB)-α) and by up-regulation of apoptosis inhibitors such as survivin. Mutations of H-RAS are observed in carcinoma ex-pleomorphic adenoma, in adenocarcinoma and in almost half of MECs, where the frequency of H-RAS mutations parallels tumour grade. Cyclin D1 seems frequently overexpressed in AdCC and MEC and correlates with prognosis. In MEC, high-cyclin D1 expression follows inactivation of secreted frizzled-related proteins (SFRPs) by hypermethylation. Nuclear pSTAT3 expression seems to play a role as tumour suppressor in the absence of EGFR, HER-2, and survivin in SGC. RUNX3, a tumour suppressor gene that, when active, facilitates TGF-beta to play its apoptotic role, appears silenced by hypermethylation in AdCC. RB1-inducible coiled-coil 1 (RB1CC1) is a positive regulator for the retinoblastoma tumour suppressor (RB1) pathway, and its expression in SGC implies better prognosis, analogous to observations in breast cancer. Efforts are underway at targeting the PI3K/AKT pathway by blocking mTOR with temsirolimus.

Pleomorphic adenoma gene 1 (PLAG1) is a specific proto-oncogene found in a large percentage of pleomorphic adenomas and is transcribed and overexpressed following a t(3;8)(p21;q12) chromosome translocation resulting in β-catenin-promoter swapping. This causes deregulated expression of PLAG1 target genes by the IGF-II/IGFIR mitogenic signalling pathway. Another fusion oncogene, MEC translocated 1 gene with exons 2–5 of the mastermind-like gene (*MECT1-MAML2*), t(11;19)(q14-21;p12-13) is transcribed into a fusion protein that was initially thought to be exclusive for low-grade MEC. However, high-grade fusion-positive MEC cancers associated with advanced-stage lethal disease have now been described. For AdCC, a recurrent reciprocal translocation of t(6;9)(q22-23; p23-24) resulting in fusion gene partners comprising *MYB* gene and the transcription factor NFIB (previously reported in AdCC of breast and, lacrimal and ceruminal glands) has now been described. In both fusion-positive and a subset of fusion-negative AdCCs, high expression of the transcript Myb was found, suggesting this to be a potential target for new therapies.

Proteins involved in DNA damage repair

p53 and ERCC1 (excision repair cross-complementation group 1) belong in this category. p53 expression and p53 mutations in AdCC are generally associated with worse outcome, but a large Finnish multivariate analysis failed to confirm additional value over a clinicopathological multivariate model. This large study however did not focus on the AdCC subgroup but studied all histological types.

Proteins involved in apoptosis

The Bcl-2 group contains pro-apoptotic proteins such as Bax, Bad and Bak and anti-apoptotic proteins such as Bcl-2, Bcl-xL and survivin. Low expression of Bcl-2 corresponds to higher apoptosis and thus better prognosis, whereas high Bcl-2 expression in SGC relates to poor prognosis and advanced T and N classification. Nuclear survivin expression indicates SGC with worse prognosis.

Proteins involved in cell-cell adhesion (hemidesmosome proteins B180 and B230, E-cadherin, CDH12, α-catenin), migration (matrix metalloprotease, heparanase) and epithelial-mesenchymal transition (NBS-1 and snail) Estrogen, progesterone and androgen receptors

Estrogen receptors have been described in AdCC, whereas androgen receptors are the target of hormonal therapy in SDC.

Microarray technology gives a tumour-specific overview of over- and underexpressed tumour genes, and can be used as a prognostic blueprint of a tumour.

This guides treatment for other tumours such as breast cancer, but to date there have been only limited efforts in SGC. An application of this strategy in AdCC resulted in the identification of a novel oncogene in salivary gland oncogenesis, AQP1, the transcription of which seems epigenetically regulated by (hypo-)methylation status.

Viral aetiology

EBV has been implicated in the genesis of bilateral Warthin's tumours and undifferentiated SGC. CMV infection in mice and in humans seems related to MEC development. This awaits further validation in larger series, but the authors found the CMV protein expressed in almost all cases studied.[17] Other viruses implicated in this disease are HPV, human herpes virus 8 (HHV-8).

SPECIFICS OF THE MAIN HISTOTYPES

In population-based studies of parotid carcinoma, the majority of carcinomas are AcCC (15–17%), followed by AdCC (16–27%) and MEC (14.5–19.2 %).[8, 40] The distribution in submandibular gland cancer and MiSGC is different, with an emphasis on especially AdCC, more than MEC and ACNOS (**Table 10.4**).

TABLE 10.4 Distribution of the major histological tumour types in minor salivary gland carcinomas[122]*

Authors	No. of patients	AdCC %	MEC %	ACNOS %	CAN %	Others %
Spiro et al.[56]	378	34	34	21	1	10
Sadeghi et al.[76]	117	59	25	15	0	1
Garden et al.[67]	160	71	16	11	1	1
Anderson et al.[68]	95	43	26	26	3	0
Parsons et al.[63]	95	60	15	22	–	–
Chou et al.[59]	256	32	38	16	3	14
Jones et al.[135]	103	70	19	–	1	9
Le et al.[58]	54	59	13	28	–	–
Vander Poorten et al.[11]	55	40	16	16	6	16
Terhaard et al.[73]	157	42	23	22	6	6
Pires et al.[136]	546	15	52	9	9	15
Loh et al.[158]	171	47	23	19	–	–
Kruse et al.[159]	27	48	30	22	–	–
Kakarala et al.[160]	639	26	50	22	2	–
Carrillo et al.[57]	77	45	30	15	4	6
Li et al.[137]	103	47	36	–	3	15

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Acinic cell carcinoma (AcCC)

AcCC usually presents as a painless parotid lump and forms some 15–17% of parotid malignancies, yet they account for only 3% of all salivary gland tumours, indicating a clear parotid predilection.[162] Macroscopic pathology commonly shows a solitary encapsulated lesion but multilobulation does occur. This tumour arises from the acinic cells, but in 75% of AcCC more than one cell type is seen and the histological patterns described include solid microcystic, papillary cystic and follicular. All of these patterns may be seen in one individual tumour.[162] AcCC is generally considered low grade and is considered to have the best survival rate, but a high-grade aggressive subgroup (papillary cystic variety) has poorer prognosis.[71, 152, 161] AcCC has a long natural history and long-term follow-up is mandatory. Spiro found that the cure rate continued to drop from 76% at 5 years to only 55% at 15 years and other authors have found the same.[156] Clearly, this can be an aggressive tumour that should be treated accordingly – early attempts at enucleation yield disastrous survival figures.[163, 165] It is generally accepted that one should not hesitate to use post-operative radiotherapy, which can only be omitted for low-stage AcCC in absence of adverse prognostic factors.[83, 92, 110]

Mucoepidermoid carcinoma (MEC)[122]

Whereas AdCC is the most frequent MiSGC overall, MEC is the most frequent type at the intraoral subsite. MEC represents about 16–37% of all MiSGCs, but about 36–59% of intraoral MiSGCs. As in many salivary malignancies the tumour is formed of several cell types, in MEC there are mucus-secreting cells, epidermoid cells and intermediate cells. The prognosis of MEC is mainly influenced by clinical stage, histological grade, and surgical margins, all strongly interrelated factors. In grading MEC, two- and three-tiered systems have been advocated. Batsakis et al.[162] follow the suggestion of Healey et al.[148] for a three-tiered system, based mainly on the involved cell types. Healey found in univariate analysis that recurrence rates of low- and intermediate-grade carcinomas are quite similar with a recurrence rate of 6% and 20% for low- and intermediate-grade MEC respectively, vs. 78% for high-grade carcinomas. The Armed Forces Institute of Pathology (AFIP) also proposed a three-tiered grading system, based on different criteria, and promoted a more quantitative approach but the clinical data supporting this complicated grading system are not convincing. Brandwein et al. showed a good correlation of these AFIP grades with stage and local control, but revealed a significant grading disparity among five experienced oral pathologists using the 'standard AFIP grading criteria'.[132]

More appealing to clinicians are simpler two-tier grading systems. Evans[150] suggests that >90% solid tumour in MEC indicates a high-grade histology, with only univariate analysis supporting this; Ciccolallo et al. suggest that >90% epithelial cells should be interpreted as high-grade histology, supported by the observation that patients with low-grade tumours have a 5-year survival of 96% whereas high-grade tumours show a death rate 10 times this. Recent large studies find no prognostic difference between low- and intermediate-grade MEC.[167] To summarize, in clinical practice only the low-grade subgroup without further negative prognostic features should be managed with surgery alone. In the intermediate-grade MEC group many patients will have additional negative prognostic factors (e.g. involved surgical margins or soft tissue invasion) that will be an indication for adjuvant radiotherapy.

Adenoid cystic carcinoma (AdCC)[122]

AdCC demonstrates insidious growth over many years, with a tendency for local recurrence and distant metastasis despite aggressive therapy at the primary site. Some patients have severe pain due to nerve invasion, and in the parotid gland VIIN palsy may be evident. In a study from Liverpool dealing with 108 patients with AdCC, nearly one-third occurred in the major salivary glands, and most of the remainder involved the minor glands.[168] Forty per cent of patients had oral cavity tumours and half of these were in the hard palate. Of all tumours 41% were locally advanced at presentation and 11% had distant metastases. Interestingly, revision of the pathology slides led to 15% reclassification as PLGA. In the Netherlands' series, 17% of the parotid cancers were AdCC, as were 40% of the cancers of the submandibular gland.

AdCC thus mainly occurs in the MiSG, where it is the most common subtype (32–71%) and, as shown in **Figure 10.2**, occurs mostly in the palate followed by the paranasal sinuses (14–17%). This tumour will often be diagnosed at an advanced stage, and due to the complex anatomical area in the skull base region, complete excision is frequently impossible[169] and further complicated by the propensity of AdCC for perineural extension, both in the MiSG, and in the parotid and submandibular glands, where large nerves are closely adjacent to the tumour. This perineural growth is notorious for skip lesions, for example, in the VIIN, isolated AdCC deposits can be observed several centimetres from where tumour invasion apparently terminated, both on frozen section and on later paraffin-section histology. The feature 'perineural growth' implies a worse prognosis.

A study from the University of Michigan showed 80% positive margins in operated skull base AdCC cases, even with tumours where experienced surgeons pre-operatively had the feeling they could resect the tumour with clear margins.[166] Every AdCC should be considered a 'clinically high-grade malignant neoplasm': the behaviour of AdCC is relentless and the long-term course is marked by multiple local recurrences, uncommon regional and yet frequent distant metastatic spread to the lungs and bones. It is often said that cure is never achieved in this disease. Sometimes optimistic 5-year survival rates are reported (e.g. 92% in an Australian series),[169] but 10- and 20-year survival rates continuously drop (e.g. in a UK series 40% at 20 years and continuing to drop until 30 years; the actuarial primary site recurrence rate in that study was 100% recurrence at 30 years,[168] and 54% in the Australian series). In a large European study, 10 years survival was 65%.[171]

AdCC uncommonly presents with lymph node metastasis, and recently an interesting hypothesis has been developed to explain this phenomenon. AdCC does produce only very limited amounts of VEGF-C, which translates into very few lymphatic vessels within the tumour due to a reduced interaction with VEGFR-3.[172]

AdCC frequently metastasizes to bone and liver, but most frequently to the lung, in approximately 70% of patients in most series. The latter metastases, although alarming to the oncologist and the patient, frequently grow slowly. A Japanese study analyzed 30 patients where 21 had pulmonary metastases, 4 of these at presentation and 17 during follow-up, and showed a cumulative incidence of distant metastasis in 100% of patients followed for longer than 5 years, regardless of grade and initial stage.[173] The average tumour doubling time of a metastatic deposit was just over one year, which is very slow, compared with lung metastases from other cancers. This tumour doubling time suggests that distant metastasis is often present long before the initial diagnosis of the primary salivary gland tumour, and this obviously puts in perspective the limits of ablative surgery for AdCC in the head and neck.

As stated above, AdCC can be graded histologically. The scheme proposed by Szanto et al.[144] indicates a primarily cribriform or tubular tumour as grade I; tumours with less than 30% solid component are grade II and tumours with greater than 30% solid component are grade III. In patients treated similarly, a solid histological pattern of AdCC carries a worse prognosis in terms of distant metastases and long-term survival on univariate analysis. In multivariate analysis, when including stage at presentation, this prognostic effect is less clear, yet a Brazilian study recently confirmed solid histology as an independent prognostic factor.[174]

Polymorphous adenocarcinoma (PAC; formerly polymorphous low-grade adenocarcinoma (PLGA))[122]

PAC, prior to 1983 considered a low-grade variant of AdCC and initially also referred to as terminal duct adenocarcinoma, has a less aggressive biological behaviour compared to other types of adenocarcinoma. About 75% of these tumours arise from MiSGs. Major salivary gland involvement is relatively unusual. It most frequently arises on the palate. Despite the better prognosis, local recurrence even with negative margins, regional recurrence and distant metastasis have all been described. Recurrence can occur very late in follow-up: in one series, local recurrences occurred at 15 years and regional recurrence occurred at 20 years after initial treatment. Therefore, the term 'low-grade' is omitted in the most recent WHO classification, which now talks about 'Polymorphous Adenocarcinoma'. There are four histological patterns: tubular, cribriform, papillary and lobular, and because of this variable appearance, P(LG)AC may be mistaken for pleomorphic adenoma or other benign tumours, and for AdCC, due to comparable growth patterns and to the presence of neurotropism. Immunohistochemical and molecular biological studies may help to differentiate these two lesions.

Adenocarcinoma NOS

This histology also forms a large subgroup in major series (8–18% of parotid carcinoma), but this proportion

depends on the effort by pathologists to revise the material. A substantial part of the tumours initially classified as adenocarcinoma not otherwise specified (ACNOS) can be specified as one of the subtypes in **Table 10.2** upon revision using modern histopathological techniques.[34, 40, 73] Nonetheless, frequently the remaining ACNOS are aggressive, with advanced locoregional extension at diagnosis and frequently implying perineural growth and positive resection margins.[41]

Carcinoma ex-pleomorphic adenoma

These tumours account for up to 5–25% of all SGC and tend to arise in the major glands.[9, 37, 112, 175] The risk of developing this carcinoma within a pre-existing pleomorphic adenoma increases with the time a pleomorphic adenoma exists, to as much as 10% by 15 years. Carcinogenesis seems associated with frequent earlier attempts at removal of a recurrent benign pleomorphic adenoma, the reason why optimal initial surgery is so much stressed upon in trainee surgeons.[177–179] The tumour may be malignant from onset or carcinomatous transformation can occur.[179] In recurrent pleomorphic adenoma, the rate of carcinoma found ranges from 7% to 16%.[177, 178, 180] In the 2005 WHO classification, for the previous term 'carcinoma ex-pleomorphic adenoma' a distinction is made between carcinoma in pleomorphic adenoma (which can be a nidus of non-invasive carcinoma in pre-existent pleomorphic adenoma or a true invasive carcinoma), the very rare and aggressive carcinosarcoma, and the metastasizing mixed tumour, in which metastases contain typical benign structures. The prognosis of a carcinoma in pleomorphic adenoma is poor: the MSKCC cause-specific survivals for this disease are 40% at 5 years, 24% at 10 years and 19% at 15 years.[181]

KEY POINTS

- The histopathological workup of SGC, i.e. typing and grading, is among the most complex areas in histopathology.
- This holds for the light microscopic, immunohistochemical and molecular biological aspects of the histopathological workup.
- Enormous advances in SGC molecular biology in the last two decades have resulted in better prognostic fine-tuning, but to date have not resulted in advances in treatment, nor in improved treatment results.

POST-OPERATIVE RADIOTHERAPY

Parotid and submandibular salivary gland malignancies

Following resection and classical histological and molecular biological workup, post-operative radiotherapy is frequently indicated in patients with salivary gland cancers. In the past, these cancers were believed to be 'radioresistant'. As an example, for submandibular gland carcinomas, Conley stated in the early 1970s[52] that there was no indication that irradiation should be given when an adequate operation has been performed; thus, only 12% of his patients were treated in a combined fashion, and there are reports of series advocating radiotherapy in less than 3% of surgically treated patients.[116] In contrast, in the Netherlands' Cancer Institute series, 67% received combined treatment, as did 59% of patients in the Princess Margaret Hospital series, Toronto, with significant reported improvement in locoregional tumour control.[54] Post-operative radiotherapy to the primary tumour used to be delivered by conformal wedged-pair beams to a dose of 60 Gy[44, 73, 110, 182, 183] but has been replaced by 3-dimensional (3D) conformal radiotherapy and lately intensity-modulated radiotherapy (IMRT), which is now considered the 'standard of care'.[184, 185]

Radiotherapy is indicated in advanced stage disease (stage III and IV) and in the presence of histopathological adverse prognostic factors. Lacking randomized trials, the evidence for this approach comes from retrospective reports, with a bias of selecting prognostically negative patients for combined therapy, yet demonstrating improved locoregional control in the combined treatment group.[51, 70, 110, 185–187] The study of the Dutch Head and Neck Oncology Cooperative Group illustrates this by a relative risk (RR) for local recurrence in surgical patients being 9.7 times the risk of patients receiving combined surgery and radiotherapy. These findings are consistent with the older matched pair analysis by Armstrong et al., describing a significantly improved DSS and local control in patients with stage III and IV disease treated with radiotherapy following resection.[108] Post-operative radiotherapy can only be omitted for stage I-II lesions in AcCC and low-grade MEC if complete resection does not reveal other adverse pathological factors (close surgical margins, perineural or perilymphatic invasion, or recurrent disease).[41, 55, 83, 92] For high-risk major salivary gland carcinomas, two reports recently documented the benefit of a post-operative platinum-based concomitant chemoradiation scheme.[188, 189]

Minor salivary gland cancer

Once the MiSGC has been resected and pathologically staged and graded, post-operative radiotherapy to the primary site is recommended for most patients. Only in 'clear margin' early stage disease (stage I and II) without lymphovascular or perineural invasion (a set of conditions usually restricted to low-grade variants), can post-operative radiotherapy be omitted without loss of disease control[11, 73, 110, 122, 125] Adverse prognostic factors, such as positive or close surgical margins,[67, 76, 125, 131] a high-grade histology,[60, 67, 125] perineural growth (particularly 'named' nerve invasion),[75, 125, 190, 191] bone and muscle invasion, paranasal sinus localization, and high T- and N-classification,[11, 67] are indications for post-operative radiotherapy. In addition to what has been said for the major salivary gland cancers, for MiSGC, proton-beam radiotherapy may be considered to reduce the risk of damage to the brain and visual apparatus in patients with

cancers involving the nasal cavity and paranasal sinuses. Improved locoregional control does not invariably lead to higher survival rates. Spiro et al.[56] were unable to demonstrate a survival benefit for patients receiving post-operative radiotherapy after matching for stage, site and histology. The unaffected incidence of distant metastases is the probable explanation: 36% of patients in the series by Garden et al, with good local control following combined treatment, eventually developed distant metastases.[67]

RADIOTHERAPY AND CHEMOTHERAPY IN UNRESECTABLE DISEASE[92, 122, 192]

Primary radiotherapy is indicated for patients who are inoperable, who refuse surgery, or who have an unresectable tumour. Unresectable SGC or resectable cancer in poor surgical candidates is controlled by conventional photon radiotherapy, with disease control rates from 17 to 57% at 10-year follow-up. The percentages at the upper limit of this range are found in series dealing with mainly early stage disease. Newer techniques such as IMRT promise better results, especially in combination with non-photon radiation, such as proton or carbon ion boost, where locoregional control seems to improve and toxicity remains limited.

Neutron radiotherapy reaches 5-year local control in up to 75% in unresectable disease, especially for AdCC, and this is ascribed to a reduced oxygen-enhancement factor, less variability of sensitivity through the cell cycle and decreased repair of sublethal cell damage. This option remains unattractive because of a lacking survival benefit (distant metastasis occurs in 40% of these patients after 51 months) and severe late side effects, including cervical myelopathy, sensorineural hearing loss, and necrosis of the soft tissues, the mandibular and temporal bone and the temporal brain lobe. Recently, the University of Washington neutron irradiation team reported even better long-term local control after giving a boost using the gamma knife at the end of neutron radiotherapy. Reports have also been published on the use of concurrent chemo-radiation for unresectable disease, showing good tumour control but with acceptable morbidity. Unfortunately, these are reports of small series and not randomized clinical trial data. For recurrent MiSGC, there have been reports on combining re-irradiation with concomitant chemotherapy, resulting in locoregional control of 72% at one year and on combining re-operation with intra-operative radiotherapy.[192]

Currently, chemotherapy remains of palliative use only in salivary gland cancer. A temporary complete remission in about 20% seems the best achievable at the moment. In metastatic ACNOS, high response rates are observed with cisplatin, doxorubicin and cyclophosphamide. Unfortunately these responses are generally short-lived. **Table 10.4** lists the explored targeted therapies that have so far been used clinically; unfortunately, none has significantly improved results. A recent high-quality meta-analysis focusing on AdCC reaches the same conclusion. In this study the activity of cytotoxic drugs given in combination was studied in 143 patients enrolled in 17 trials. In 14 studies, cisplatin-based regimens led to objective responses in 29 of 118 patients (response rate 25%). Response duration ranged from 6 to 77 months.[195] Recent phase II studies explored the combination of cytotoxic and targeted therapy (imatinib and cisplatin, and bortezomib and doxorubicin) in AdCC and concluded that the results warrant further investigation of this approach.

KEY POINTS

- Post-operative radiotherapy is a proven adjunctive treatment to surgery in the management of SGC and has a proven effect on locoregional control in most patients.
- Of all head and neck neoplasms, for SGC treatment, the recent (r)evolution towards IMRT has probably its greatest merits in improving dose delivery to the target volume, while minimizing 'collateral damage' to the non-involved surrounding healthy tissues.
- In SGC, cytotoxic chemotherapy and targeted therapies remains experimental and should be tested in clinical trial settings; to date most are of a palliative use only.

TREATMENT RESULTS AND PROGNOSIS ACCORDING TO SITE

Major salivary gland cancer: Parotid[92]

Treatment results in major treatment centres have to be appreciated in their specific context of stage, percentage high-grade, treatment period and corresponding treatment regimens, patient inclusion criteria and adequacy of follow-up (**Table 10.5**). The decision to exclude palliative intent patients in the 1999 Manchester series,[99] results in a patient cohort with relatively low stage (1 in 5 patients in Stage III-IV) and high DSS as opposed to the 1999 Amsterdam series that includes palliative patients, increasing the proportion of advanced stage disease (1 in 4 in stage IV), reflected in a lower overall DSS.[41]

Many univariate and multivariate statistical analyses have focused on identifying prognostic factors in SGC. Variables such as histological subtype,[72, 195] grade, stage, age, gender, pain, skin invasion and VIIN dysfunction, resection margins and comorbidity have been identified as statistically significant prognostic factors. Several outcomes have been used as the dependent variable, including overall survival, DSS and recurrences. However, it is difficult to meaningfully communicate the data from these disparate studies in a clinical setting.

To empower the consultation and enable effective communication of prognosis, the authors have designed a prognostic index combining several important patient and tumour-specific prognostic factors, appropriately weighted, to provide a point estimate of tumour recurrence. We constructed such an index from the Dutch

TABLE 10.5 Disease-specific survival (DSS) for parotid carcinoma

Research group	Publication year	Number of patients	DSS 5 y	DSS 10 y
Spiro[9]	1986	623	55%	47%
Spiro et al.[71]	1989	62	63%	47%
Kane et al.[10]	1991	194	69%	68%
Poulsen et al.[205]	1992	209	71%	65%
Leverstein et al.[38]	1998	65	75%	67%
Therkildsen et al.[205]	1998	251	76%	72%
Renehan et al.[99]	1999	103	78%	65%
Vander Poorten et al.[41]	1999	168	59%	54%
Harbo et al.[207]	2002	152	57%	51%
Godballe et al.[208]	2003	85	52%	
Vander Poorten et al.[40]	2003	231	62%	
Lima et al.[209]	2005	126	72%	69%
Mendenhall et al.[210]	2005	224		57%
Vander Poorten et al.[34]	2009	237	69%	58%
Guntinas-Lichius et al.[211]	2015	295	82%	82%

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patient population for the situation before (PS1) and after (PS2) surgical treatment. When the requisite data is input into the prognostic equation, the resultant score places the patient in one of four prognostic groups. This prognostic index has been validated in a nationwide and in an international database, indicating its usefulness in parotid carcinoma patients in general. It is available online at (www.uzleuven.be/parotid).[34] A recent validation effort in a Brazilian population did not show the index to have similar prognostic accuracy, but a critical analysis of the population and the methods used identified several reasons for this lack of concordance.[196]

Since the discovery of molecular biology in salivary gland research, it is likely that this new information will contribute to the prognosis. Batsakis rightly commented 26 years ago that critical multivariate assessment of putative molecular biological, clinical and pathological factors with rigorous validation will be needed.[140] Ideally this exercise should be done on a large multicentre datasets.[171]

Submandibular salivary gland

With the use of adjuvant radiotherapy, treatment results for submandibular gland cancer have improved in recent publications.[9, 116] The 5-year survival rate of 50% and the 10-year survival rate of 36% in the series of the Netherlands' Cancer Institute are comparable to the results of a nationwide analysis[6] showing a 5-year survival rate of 52%.[117, 118] An exceptionally high figure was described by Weber et al, who reported a 5-year survival rate of 69% in a population with a surprising majority of T4b disease.[53] The 5-year DSS of 61% and the 10-year DSS of 51% in Amsterdam are almost similar to the findings in Toronto with a 5-year DSS of 60% and a 10-year DSS of 48%. In the past, submandibular gland cancers were ascribed a worse prognosis than their parotid counterparts.[9, 116, 197] Recent studies[51, 70, 71, 198, 199] and our own experience[55] do not support this stance.[122]

Negative prognostic factors for survival, DSS and locoregional control are increasing age at diagnosis,[54, 55] TNM stage,[53, 54, 116–118] extra-glandular soft-tissue extension[53–55] and perineural growth.[55] As for other sites, the finding of a better locoregional control in patients with negative prognostic factors treated with surgery and adjuvant radiation evidence for the efficacy of post-operative radiation.[51, 53, 54, 70, 108, 198]

MiSG cancer[122]

Published overall survival rates vary widely, with 5-year survival ranging from 66% to 80% and 10-year survival ranging from 56% to 70%. This wide range is attributed to differences in non-tumour related deaths, referral bias and selection bias. Selection bias occurs when comparing overall results of all localizations to those of only oral or palatal MiSGCs, known to present at lower stages. Short follow-up periods do not capture long-term treatment failures. In the Netherlands' Cancer Institute series recurrences appeared up to 139 months after treatment (median 23 months). All recurrences after 5 years were in patients with AdCC. Bias can also be caused when patients with prior treatment or delayed referral, or distant metastases are excluded.

Initial tumour control after therapy is expected to be 56–62%. Distant metastasis from MiSGC in patients who are M0 at presentation seems to follow a '1 in 5 rule'. i.e. 20% of patients will develop M+ disease during follow-up.[11, 56, 76] MiSGCs overall do not imply a worse prognosis than their submandibular and parotid counterparts,

although specific involvement of subsites (e.g. the skull base) are associated with a worse outcome.

Clinicopathological prognostic factors[122]

Many univariate and multivariate statistical analyses have focused on prognostic factors in MiSGC to relate the individual's prognosis to the overall results. For example, decreasing overall survival parallels increasing age at diagnosis, but this difference is less clear for DSS where patients dying of other causes are not considered as treatment failures. Also for tumour control, the studies that include age as a prognostic parameter do not retain it as having a prognostic effect, so age alone should not determine treatment policy. In a cohort that also includes major SGC, comorbidity remained an independent factor.[201] As stated before, when a MiSGC arises in the nose, paranasal sinuses, or nasopharynx, very poor treatment results have been observed. This relationship of site to prognosis is most likely confounded by stage. Treatment of late-stage skull base MiSGC is complicated by poor surgical access. UICC Stage determines prognostically separate groups for survival, DSS and tumour control. T-classification alone also predicts all outcomes, as does increasing N classification and M1 classification.

Histologically, soft-tissue invasion including perineural and vascular invasion by the primary tumour are negative prognostic factors, as is the strongly related factor radicality of resection. The problem of surgical access to MiSGC results in a high percentage of close or positive margins, ranging from 23% or 27%[11, 137, 201] up to 40%.[67] When looking at specific sites for specific types, margins are reported in up to 80%.[170] In a homogenous series of 67 patients with oral MiSGC, multivariate analyses showed that clinical T-status, anatomical subsite and margin status were independent predictors for overall survival; T-status and margin status were independent predictors for locoregional recurrence-free survival.[202] Histopathological high grade is strongly correlated with these features. Independent prognostic power is sometimes lost due to its strong interrelationship with other negative prognostic factors. The most frequent histological type, AdCC, is considered a clinically high-grade tumour by most authors. According to da Cruz Perez et al,[199] clinical stage, solid-growth pattern and expression of p53 were the most important prognostic factors in children with AdCC. It is unclear whether grading of AdCC is useful in patient management. There is morphological overlap between solid conventional AdCC and high-grade transformation, and the transition from conventional AdCC to high-grade transformation is often gradual. Basically, the aggressive features common to both variants are more exaggerated in high-grade transformation, while solid conventional AdCC shows only slight deviation from tubular or cribriform patterns.[85, 203] Costa et al have studied the genetic profile of AdCC with high-grade transformation (HGT) versus solid type, and concluded that AdCC-HGT may not necessarily reflect a more advanced stage of tumour progression, but rather a transformation to another histological form in which the poorly differentiated forms presents a genetic complexity similar to the solid AdCC.[204] Although not frequently encountered, neck metastasis also heralds poor DSS. All of previously mentioned clinicopathological factors have been considered for their ability to predict the outcome 'positive neck disease' in a recent large-scale analysis of the Surveillance, Epidemiology, and End Results (SEER) database. The analysis yielded a simple prognostic index including the factors male gender, T3-T4 classification, pharyngeal origin of the MiSGC, and high-grade for adenocarcinoma and MECs. However, this index still needs validation.[123]

KEY POINTS

- Treatment results for both major and minor SGC are comparable and in the range of 60–70% 5-year survival and 50–60% 10-year survival.
- For an individual patient, this expected treatment result varies highly depending on an extensive list of patient-, tumour-, and treatment-related prognostic factors.
- For parotid cancer, prognostic estimates can be performed using validated online calculators.
- For submandibular and MiSGC, the clinician is dependent on the published literature to 'guess-timate' the expected outcome following treatment.

COMPLICATIONS OF TREATMENT

Parotid gland surgery[205]

The typical complication for parotid surgery is temporary or permanent facial palsy, but in experienced hands, normal function can be achieved in 96% of patients after superficial parotidectomy. Further complications are haemorrhage, infection, skin necrosis, Frey syndrome and salivary fistula.

Frey syndrome is rarely encountered in parotid cancer patients, as most of them receive radiotherapy, inhibiting its development. Treatment of this condition with topical anticholinergics is usually unsuccessful owing to poor compliance. The current treatment of choice is chemodenervation using botulinum toxin type A. The median effectiveness is 8–11 months and the treatment can be repeated. Interposition grafts that have been proposed as preventive strategies include the sternocleidomastoid muscle flap. Although there are opponents, this flap is considered effective by most clinicians. In malignant pathology there is a drawback to its use as it complicates revision surgery if needed. The same remark holds for the superficial musculoaponeurotic system (SMAS) flap, reported to be quite effective in prevention of Frey syndrome. Interposed foreign material has an unacceptable rate of complications (haematoma, seroma and salivary fistula).[206]

Paresthesia in the GAN area occurs in 57% of patients after sectioning the GAN, but 90% of patients do not report this to be cumbersome with no impact on quality of life is reported.[208] Recent evidence suggests that the posterior branch of the GAN can be saved in 2/3 of patients undergoing parotidectomy, at the expense of little extra

surgical time, resulting in sensibility returning to normal in 80–100% of patients. Furthermore, the preserved GAN can be a good interposition graft for VIIN reconstruction in surgery for malignant disease.[92]

Submandibular gland surgery

Typical surgical complications of submandibular gland cancer relate to the nerves that may have to be sacrificed in the removal of the submandibular gland for malignancy. Nerves at risk are the mandibular and cervical branches of the facial nerve, the hypoglossal nerve and the lingual nerve. Normally, the lower facial branches should not be damaged unless they loop particularly inferiorly to the mandible or a wide excision of soft tissue is necessary. Neuropraxia resulting from traction is the commonest cause of this problem; recovery is rare. Sacrifice of the hypoglossal nerve leads to paralysis of one side of the tongue but functional adaptation is good and rarely causes severe problems. Damage to the lingual nerve is less likely as it is high up behind the mandible but if damage does occur it is potentially a serious problem as the loss of sensation allows repeated trauma to the tongue from dentition. Repair tends to be unsuccessful.

Radiotherapy

Radiotherapy complications include mucositis, skin ulceration, hair loss, mandibular and temporal bone osteoradionecrosis, fibrosis, cerebral radionecrosis, hearing loss (sensorineural and conductive due to refractory external otitis) and xerostomia. With the advent of IMRT some of these complications can be abrogated.[122]

CONCLUSION

Salivary gland cancer is a particularly demanding tumour for both patient and the multidisciplinary team. Every step in the management algorithm is complicated: the clinical and radiological evaluation, the histological diagnosis, the ablative and reconstructive surgery, the adjuvant radiotherapy and the management of complications. The best care can undoubtedly be provided when these patients are centralized in specialized tertiary referral centres.

KEY POINTS

- The incidence of malignant salivary gland neoplasms in the Western world is 7 to 12 per 1,000,000 person-years.
- Salivary malignancy increases with exposure to environmental factors, low-dose ionizing radiation and aflatoxins.
- Smoking of cigarettes is related to development of Warthin's tumours.
- EBV infection may predispose to the development of Warthin's tumour and undifferentiated carcinoma.
- The smaller the salivary gland, the less frequent a tumour is likely to manifest, but when it does the more likely is the tumour to be malignant.
- Parotid tumours
  - rapid increase in size or volume, the presence of pain, enlarged neck lymph nodes, fixation to deep structures or skin, or VIIN dysfunction should alert a likely diagnosis of malignancy
  - tumour imaging aims to estimate the extent (summarized in the TNM classification), location and probability of malignancy
  - MRI scanning is mandatory to evaluate invasion of the VIIth nerve, fixation to the deep structures, location at the stylomastoid foramen or deep lobe with the use of CT imaging to evaluate suspected bone invasion.
- Submandibular tumours, although frequently symptomless, are often malignant.
- MiSG tumours commonly present at an advanced disease stage and their extent is summarized as per the TNM classification for that anatomic location.
- Pre-treatment cytological assessment should be performed for major salivary gland tumours should be performed using FNAC; in selected instances UGCB can be performed, and UGCB or incisional biopsy can be considered when there is associated skin ulceration.
- Incisional or punch-biopsy for MiSG tumours is standard of care.
- The preferred treatment of parotid and submandibular gland cancer treatment is surgery.
- VIIN-preserving parotidectomy (allowing for microscopic remnant disease if unavoidable – followed by radiotherapy) in a patient with a pre-operatively functioning VIIN is considered the standard of care.
- Gross tumour involvement of the VIIN requires nerve resection followed by immediate cable grafting.
- The N+ neck requires surgery, the N0 neck should be treated electively surgically or by radiotherapy, depending on the risk factors.
- Post-operative radiotherapy improves locoregional control depending on the prognostic factors present.
- For submandibular gland malignancy, the minimally required surgery is a gland resection within a level I-II-III neck dissection (selective neck dissection); the indication for post-operative radiotherapy follows that as for parotid gland malignancy.
- The optimum curative treatment for minor salivary gland tumours is surgery.
- The surgical approach and resection should be dictated by the site of origin and can encompass the entire spectrum of head and neck surgical resective and reconstructive procedures.
- Meaningful clear-margin surgery is often impossible to achieve at certain sites because of the extensive local anatomical invasion by tumour at diagnosis (skull base and perineural invasion); in these instances, primary radical radiotherapy may be the first and only choice of treatment available.
- The histopathological workup of SGC, i.e. typing and grading, is among the most complex areas in histopathology.
- This holds for the light microscopic, immunohistochemical and molecular biological aspects of the histopathological workup.
- Enormous advances in SGC molecular biology in the last two decades have resulted in better prognostic fine-tuning, but to date have not resulted in advances in treatment, nor in improved treatment results.

- Post-operative radiotherapy is a proven adjunctive treatment to surgery in the management of SGC and has a proven effect on locoregional control in most patients.
- Of all head and neck neoplasms, for SGC treatment, the recent (r)evolution towards IMRT has probably its greatest merits in improving dose delivery to the target volume, whilst minimizing 'collateral damage' to the non-involved surrounding healthy tissues.
- In SGC, cytotoxic chemotherapy and targeted therapies remains experimental and should be tested in clinical trial settings; to date most are of a palliative use only.
- Treatment results for both major and minor SGC are comparable and in the range of 60–70% 5-year survival and 50–60% 10-year survival.
- For an individual patient, this expected treatment result varies highly depending on an extensive list of patient-, tumour-, and treatment-related prognostic factors.
- For parotid cancer, prognostic estimates can be performed using validated online calculators.
- For submandibular and MiSGC, the clinician is dependent on the published literature to 'guess-timate' the expected outcome following treatment.

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CHAPTER 11

TUMOURS OF THE PARAPHARYNGEAL SPACE

Suren Krishnan

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SEARCH STRATEGY

The data in this chapter are based on a search using the following keywords: parapharyngeal tumours, carotid body tumours and paragangliomas.

INTRODUCTION

The parapharyngeal space is an intriguing compartment of the head and neck. Although it is the site of only 0.5% of all head and neck masses, the unusual pathology and proximity to vital anatomy attracts the special interest of surgeons, radiologists and pathologists.

Early reports of these rare tumours were made by McIlrath[1] in 1963 and subsequent reports by Maran[2] in 1984, Som and Biller[3] in 1981 and Pensak and Gluckman[4] in 1994, who had series that averaged three or four cases per year. The definitive literature on the topic, describing the anatomy, pathology and surgical treatment was published by Olsen[5] in 1994. Riffat et al.[7] published a systematic review of the international literature examining the experience with 1143 parapharyngeal space tumours reported over a 20-year period in 2014.

Lesions of the parapharyngeal space may involve a wide spectrum of primary pathologies.[5,6] Pre-operative diagnostic accuracy has improved with the advent of multi-planar radiological imaging including fine-sliced computerized tomography (CT) with contrast and magnetic resonance imaging (MRI) with fat suppression sequences and gadolinium for contrast. Image-guided fine-needle aspiration cytology has improved histological diagnosis. This allows for a better understanding of the nature of these lesions and a better plan for the surgical approach to them.

There has been increasing interest and use of transoral robotic surgery (TORS) in the treatment of benign and malignant tumours of the oropharynx. TORS has the approval of the US Government's Food and Drug Administration (FDA) for use in early oropharyngeal cancers and benign lesions of the head and neck since 2009. The da Vinci surgical robotic system (Intuitive Surgical Inc., Sunnyvale, California) provides three-dimensional, high-resolution visual access with magnification as well as tremor filtration and motion scaling of robotic instruments. This allows for delicate dissection and addresses previous concerns leveled against transoral approaches to the parapharyngeal space with respect to controlled dissection around vital neurovascular structures and tumour spillage.

ANATOMY

The parapharyngeal space is a potential neck space filled with fat and areolar tissue. A variety of names have been ascribed to this space including pterygomaxillary space, pharyngomaxillary space, pterygopharyngeal space and lateral pharyngeal space. However, the term parapharyngeal space is generally accepted.

The parapharyngeal space is classically described as an inverted pyramidal-shaped potential space (**Figure 11.1**). Its base lies superiorly at the skull base and comprises

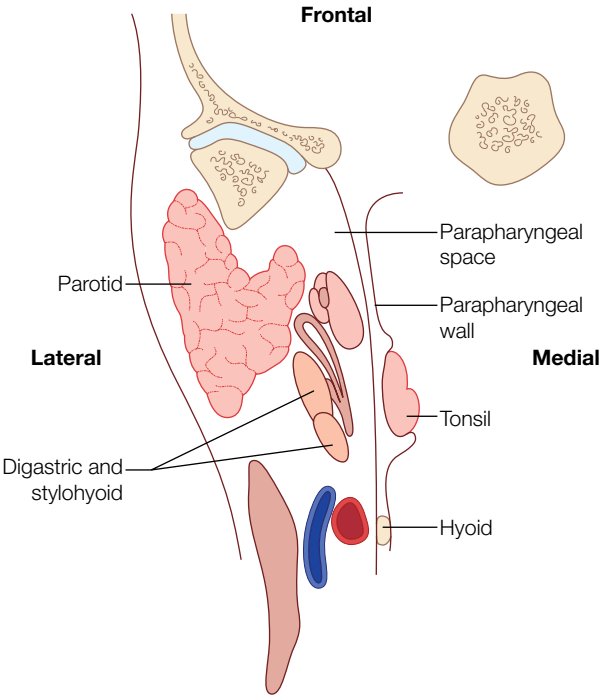

Figure 11.1 The parapharyngeal space resembles an inverted pyramid. Used with permission from Olsen KD. Tumors of the parapharyngeal space. *Laryngoscope* 1994; **104**(5) Suppl 63, Fig 1, p. 2.

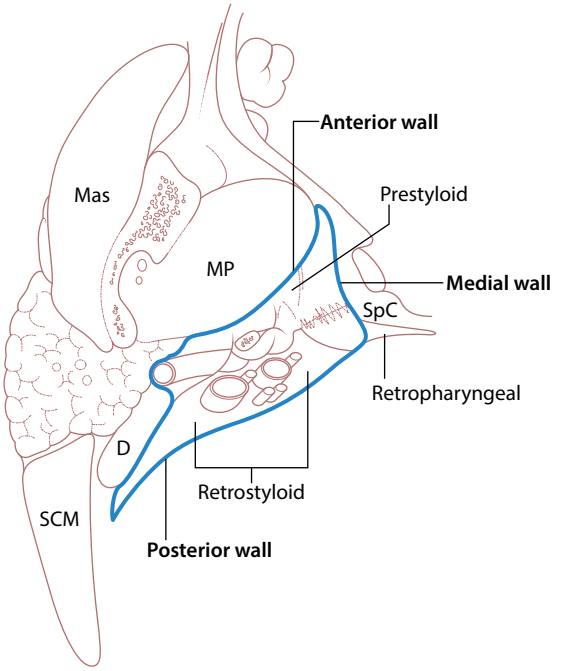

Figure 11.2 Pre-styloid and post-styloid (retrostyloid) compartments separated by condensation of fascia – the aponeurosis of Zuckerkandl and Testut. P, parotid gland; D, digastric; MP, medial pterygoid; Mas, masseter, SCM, sternocleidomastoid. Used with permission from Olsen KD. Tumors of the parapharyngeal space. *Laryngoscope* 1994; **104**(5) Suppl 63, Fig 3, p. 4.

the sphenoid and temporal bones. This area includes the jugular and hypoglossal canal and the foramen lacerum. Its apex lies inferiorly at the greater cornu of the hyoid bone. It has three sides, medial, lateral and posterior and an anterior leading edge which is the pterygomandibular raphe.

The medial surface is distensible and comprises the superior pharyngeal constrictor muscle, the buccopharyngeal membrane and the pharynx. The lateral surface, which is relatively immobile, comprises the medial pterygoid muscle, the ramus of the mandible, and the deep lobe of the parotid gland, and below the level of the mandible, the lateral aspect is bordered by the fascia of the posterior belly of the digastric muscle. It has a posterior surface which is part of the prevertebral fascia, bordered by the carotid sheath posterolaterally and the retropharyngeal space posteromedially.

Two fascial condensations in the parapharyngeal space are of surgical importance. First, the parapharyngeal space is divided into two parts by the fascial condensation called the aponeurosis of Zuckerkandl and Testut (**Figure 11.2**). This fascia joining the styloid process to the tensor veli palatini divides the parapharyngeal space into the pre-styloid and post-styloid compartments. The pre-styloid compartment contains adipose tissue, lymphatics, ectopic salivary gland tissue and small nerves and vessels, a small branch of the trigeminal nerve to the tensor veli palatini muscle and branches of the ascending pharyngeal artery and pharyngeal venous plexus. It is related to the retromandibular, deep aspect of the parotid gland. The post-styloid compartment is posteromedial and contains the internal carotid artery, internal jugular vein, cranial nerves IX to XII, the cervical sympathetic chain, lymph nodes and glomus bodies.

Second, a condensation of cervical fascia forms a band which extends from near the apex of the styloid process of the temporal bone to the angle and posterior border of the mandible (**Figure 11.3**). This stylomandibular ligament, lying posteriorly and the posterior border of the mandible, lying anteriorly, form the stylo-mandibular tunnel. The tunnel is a deep relation of the deep lobe of the parotid gland. Tumours of the deep lobe can extend into the parapharyngeal space through this tunnel giving rise to a dumbbell shaped tumour.

PATHOLOGY

As mentioned above, parapharyngeal space tumours account for 0.5% of all head and neck masses. In a comprehensive review of the literature on parapharyngeal space tumours, Riffat et al. identified approximately 70 different histological subtypes of lesions.[7] Of these 82% were benign and 18% malignant. The most common tumours were of salivary gland origin, accounting for 45% of all lesions. These arose in the pre-styloid compartment. The vast majority (75%) were benign and of these 64% were pleomorphic adenomas. Adenoid cystic carcinoma and muco-epidermoid carcinoma were the commonest reported malignant lesions.

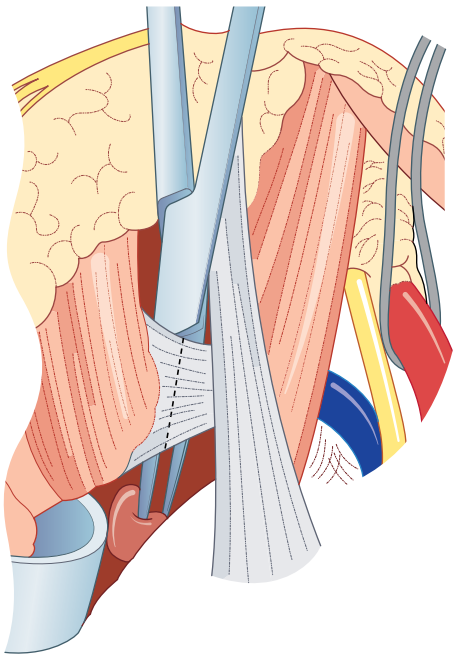

Figure 11.3 Stylomandibular ligament of the left neck from styloid process to posterior border of mandible forming the stylomandibular tunnel. Used with permission from Olsen KD. Tumors of the parapharyngeal space. *Laryngoscope* 1994; **104**(5) Suppl 63, Fig 10, p. 21.

Neurogenic lesions accounted for 41% of lesions in the parapharyngeal space. The majority of these lesions are benign and of these 52% were paragangliomas, 27% were schwannomas and 9% were neurofibromas.

Malignant lesions accounted for 5% and the majority were of neurogenic origin arising in the post-styloid space and the major subtype was malignant peripheral nerve sheath tumour.

A variety of miscellaneous lesions account for 12% of parapharyngeal space tumours. These include internal carotid artery aneurysms, branchial cleft cysts, haemangiomas and meningiomas. Metastatic lesions account for 3% of lesions and 2% of lesions are of lymphoid origin.

Salivary gland tumours

These are the most common neoplasms of the parapharyngeal space. The majority are benign and of these, the majority are pleomorphic adenomas arising from the deep lobe of the parotid gland. A small number arise from ectopic salivary glandular tissue lying in the parapharyngeal space. It is important to distinguish the difference. Tumours arising from the deep lobe of the parotid are generally not suited to contemporary transoral resection using endoscopic or transoral robotic approaches. These tumours may well require a partial parotidectomy and a transparotid and transcervical approach for resection. Parapharyngeal space pleomorphic adenomas, independent of the deep lobe of the parotid gland and arising from ectopic salivary glandular tissue, are amenable to transoral resection and despite their size are suitable for blunt dissection mobilization of the tumour from the skull base. The importance of imaging using both CT and MRI is elaborated in 'Imaging and other investigations' below. In summary, to plan surgical resection, it is important to assess the tumour's relationship to the deep lobe of the parotid gland and to understand if the tumour has a cystic component and the relative thickness of the tumour capsule.

Other benign salivary gland tumours in the parapharyngeal space include Warthin's tumours, basal cell adenomas, monomorphic adenomas, myoepitheliomas and benign lymphoepithelial lesions.

Malignant salivary gland tumours of the parapharyngeal space include adenoid cystic carcinomas, mucoepidermoid carcinomas, squamous cell carcinomas, adenocarcinomas, acinic cell carcinomas and myoepithelial carcinomas. These generally require a parotidectomy with sparing of the facial nerve dependent on pre-operative nerve function with a transcervical approach. The surgical resection may need to be extended to encompass the tumour by means of mandibulotomy for access or mandibular resection if bone is involved in the tumour or access may need to be improved by mastoidectomy or infra-temporal fossa approaches.

Paragangliomas

Paraganglia are groups of cells of neural crest origin belonging to the extra adrenal chromaffin and nonchromaffin cell system (**Figure 11.4**). They are believed to play a role in chemoreception. Paragangliomas are tumours that arise from paraganglia and head and neck paragangliomas may occur from paraganglia along the arterial vasculature and cranial nerves from the skullbase to the aortic arch. About 30% of these tumours are believed to have a genetic origin related to the *Succinyl Dehydrogense* (*SDH*) gene locus. The *SDHA*, *SDHB* and *SDHC* genes are particularly associated with familial head and neck paragangliomas. Head and neck paragangliomas may also be associated with the multiple endocrine neoplasia (MEN) syndromes MEN2a and MEN2b.

Most of these tumours present as an asymptomatic neck mass or an intraoral mass by means of medial displacement of the superior pole of the palatine tonsil. These tumours are believed to be present for months to years prior to the onset of the symptoms and many are the result of an incidental diagnosis. About 10% of paragangliomas are multicentric and should have imaging such as whole body MRI to assess other sites such as the aortic arch and adrenal. About 3% may be secretory and present with systemic symptoms associated with catecholamine release. All patients with paraganglioma should be assessed for catecholamine secretion prior to surgery to avert anaesthetic complications from catecholamine release potentially occurring during surgical manipulation of the tumour. Paragangliomas are slow-growing benign tumours and the decision to perform surgery needs to be well considered. The surgical complications from lower cranial nerve

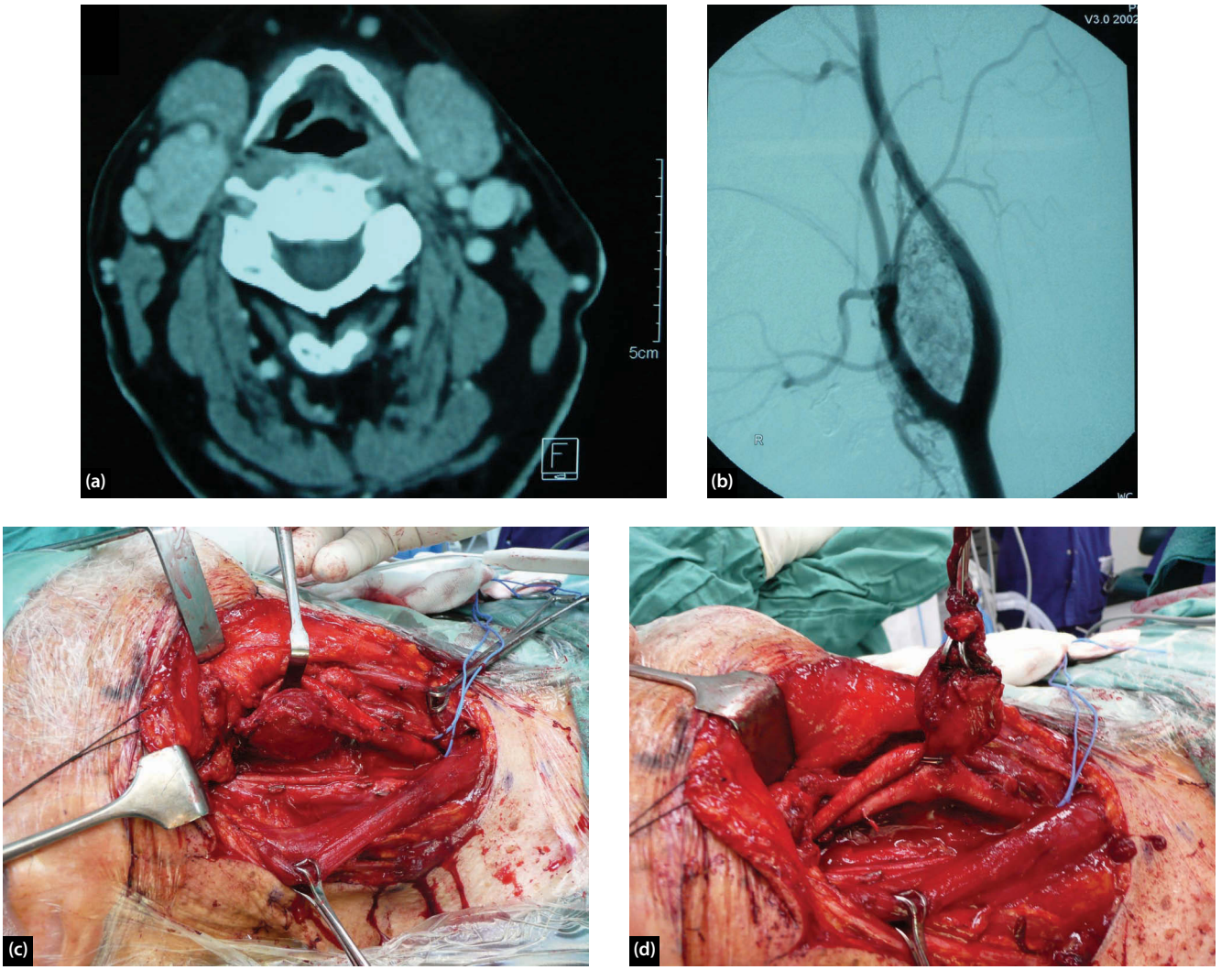

Figure 11.4 **(a)** CT neck showing vascular right carotid body tumour lying between internal and external carotid arteries. **(b)** Angiogram showing vascular right carotid body tumour splaying Internal and external carotid arteries – the 'Lyre' sign. **(c)** Right carotid body tumour. **(d)** Right carotid body tumour dissected off internal and external carotid arteries.

palsies may be more distressing than the lesion and high-vagal paraganglioma may not be amenable to complete resection without significant risk to the vagus, glossopharyngeal, accessory and hypoglossal nerves. The usual indications are suspected malignancy as evidenced by multiple lesions, erosion of adjacent bone or involvement of adjacent cranial nerves or associated regional lymphadenopathy. Surgery may also be indicated if increasing tumour size causes pressure effects on surrounding vascular and neurological structures.

It is difficult to discriminate between benign and malignant paraganglioma unless histological assessment is performed. Both malignant and benign tumours are comprised of the same two major cell types that comprise the paraganglia, these being epithelioid chief cells and sustentacular supporting cells. Together these two cell types form clusters of cells (Zellbalen), which are surrounded by extensive vascular sinusoids. Histological markers such as central necrosis, vascular invasion, and mitosis or nuclear atypia do not appear to be correlated with metastasis or true invasion.[8]

Paragangliomas have characteristic imaging features including demonstration of vascularity, the so called 'salt and pepper' appearance and in the case of carotid body tumours, a displacement of the angle between the internal and external carotid arteries known as the 'Lyre' sign Surgical resection for large lesions requires careful planning and may need transmastoid and infratemporal fossa approaches (**Figure 11.5**).

Schwannomas

Schwannomas are benign neurogenic tumours considered to originate from either Schwann cells or fibroblasts supporting the nerve. They present in patients between 30 and 70 years of age. They usually arise from either the vagus nerve or the sympathetic trunk. The vagus nerve is reported to be the origin of 50% of parapharyngeal

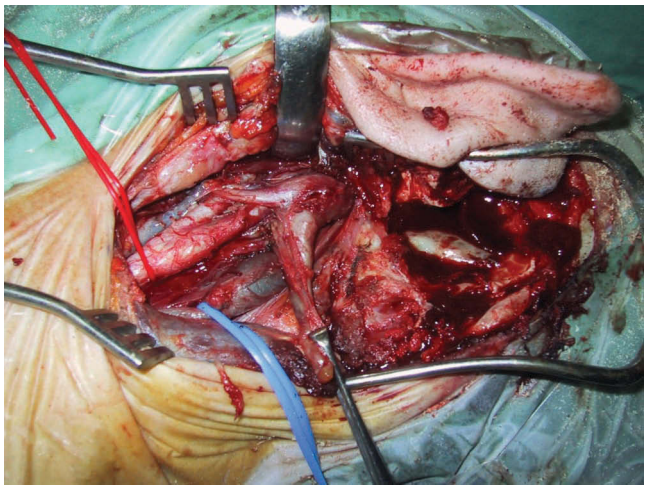

Figure 11.5 Transcervical with transmastoid approach to resect a left vagal paraganglioma. Tumour grasped by Allis forceps. Red ligature loop around carotid artery, blue ligature loop around internal jugular vein and sigmoid sinus on view in mastoid cavity.

schwannomas and cervical sympathetic chain is the next common source. Generally, schwannomas are characterized by slow and asymptomatic growth. However, progressive growth in the parapharyngeal region may result in pressure effects and cause dysphagia and hoarseness of voice. The pre-operative evaluation is critical, with imaging modalities like CT and MRI determining the diagnosis[9] and may indicate the nerve of origin.[10] These tumours are usually fusiform along the long axis of the nerve or may be round. They are of heterogenous signal intensity with hypointense, isointense and hyperintense areas on CT and MRI. Transcervical or transoral biopsy of parapharyngeal space schwannomas is usually associated with unique pain not usually reported by patients undergoing fine-needle aspiration biopsy and may be complicated by haemorrhage, infection and rarely cranial nerve injury.

Metastases to the parapharyngeal space

The parapharyngeal space contains lymph nodes and these drain the mucosa of the upper aero digestive tract and viscera of the neck. It is important to assess the nodal status of the retropharyngeal and parapharyngeal nodes when assessing metastatic neck disease in head and neck cancer. The retropharyngeal and parapharyngeal nodes are not routinely encompassed in surgical fields. However, they are accessible to both surgery and radiation when identified as being involved with metastases.

The most common metastases to the parapharyngeal space is from nasopharyngeal cancer, said to be involved in up to 30% of cases. These nodes may also be involved in tonsil and tongue base cancers and maxillary sinus cancer. Other potential primary sites include the thyroid and parotid glands. Rarely these nodes maybe involved with distant sites such as breast, colon and prostate cancer.

The parapharyngeal space may be directly invaded by malignancy from the nasopharynx, tonsil, retromolar trigone, palate and tongue base.

While benign tumours of the parapharyngeal space enjoy low levels of recurrence with a 5-year progression free survival rates of 93%, malignant tumours of the parapharyngeal space fare worse with a 5-year progression free survival rate of 61%.[11]

CLINICAL PRESENTATION AND EVALUATION

These tumours are usually asymptomatic oropharyngeal masses, found on incidental examination for innocuous symptoms such as a sore throat. They need to be at least 3 cm before they become apparent and present as a neck mass. They may present with a simple nasal obstruction or snoring, or may present with hearing loss due to Eustachian tube occlusion. Rarely they may present with cranial nerve dysfunction causing hoarseness, dysphagia or cough, which may be due to pressure on or involvement of, the hypoglossal, vagus and glossopharyngeal nerve, or Horner syndrome.

Clinical evaluation requires assessment of the airway, speech and swallowing, a full head and neck examination including cranial nerves examination, nasopharyngoscopy and examination of the middle ear for effusion. Bimanual palpation and ballotment helps assess tumour mobility and size and appreciation of the displacement of the tonsil or the posterior pharyngeal wall provides clues to whether the lesion has its origins from the pre-styloid or post-styloid compartment.[12]

IMAGING AND OTHER INVESTIGATIONS

Accurate imaging of the parapharyngeal space is essential to planning surgical resection. Multiplanar imaging with fine slice CT and MRI provides the detail required. Further information regarding vascularity and relationship to the neurovascular structures can be gained from MR angiography and carotid angiography.[13–15] Therapeutic interventions such as pre-operative embolization or balloon occlusion studies can be performed at the same time.

The parapharyngeal space appears as a small triangular space on axial imaging with an image density or signal consistent with fat. Knowledge about the displacement patterns of fat and the internal carotid artery within the parapharyngeal space will aid in the localization of lesions.

The presence of a fat plane between the parotid and a lesion differentiates a truly parapharyngeal space lesion from an extension of a deep lobe parotid lesion through the stylo- mandibular tunnel into the parapharyngeal space

(**Figure 11.6a–d**). A lesion arising in the pre-styloid space may have a rim of parapharyngeal fat antero-medially, but displaces the parapharyngeal fat and internal carotid artery posterolaterally (**Figure 11.7a,b**). However, a lesion in the post-styloid compartment will displace the parapharyngeal fat and internal carotid artery anteromedially. MRI with fat suppression sequences can help delineate this relationship clearly.

CT scans can show evidence of bony detail and erosion by these tumours and may also show calcification within tumours. MRI scans show soft-tissue extension of these tumours including intracranial extension. MRI scan with gadolinium can also show involvement of nerves and perineural spread.

Some lesions have classic imaging characteristics like congenital cysts which on CT are seen as low attenuation

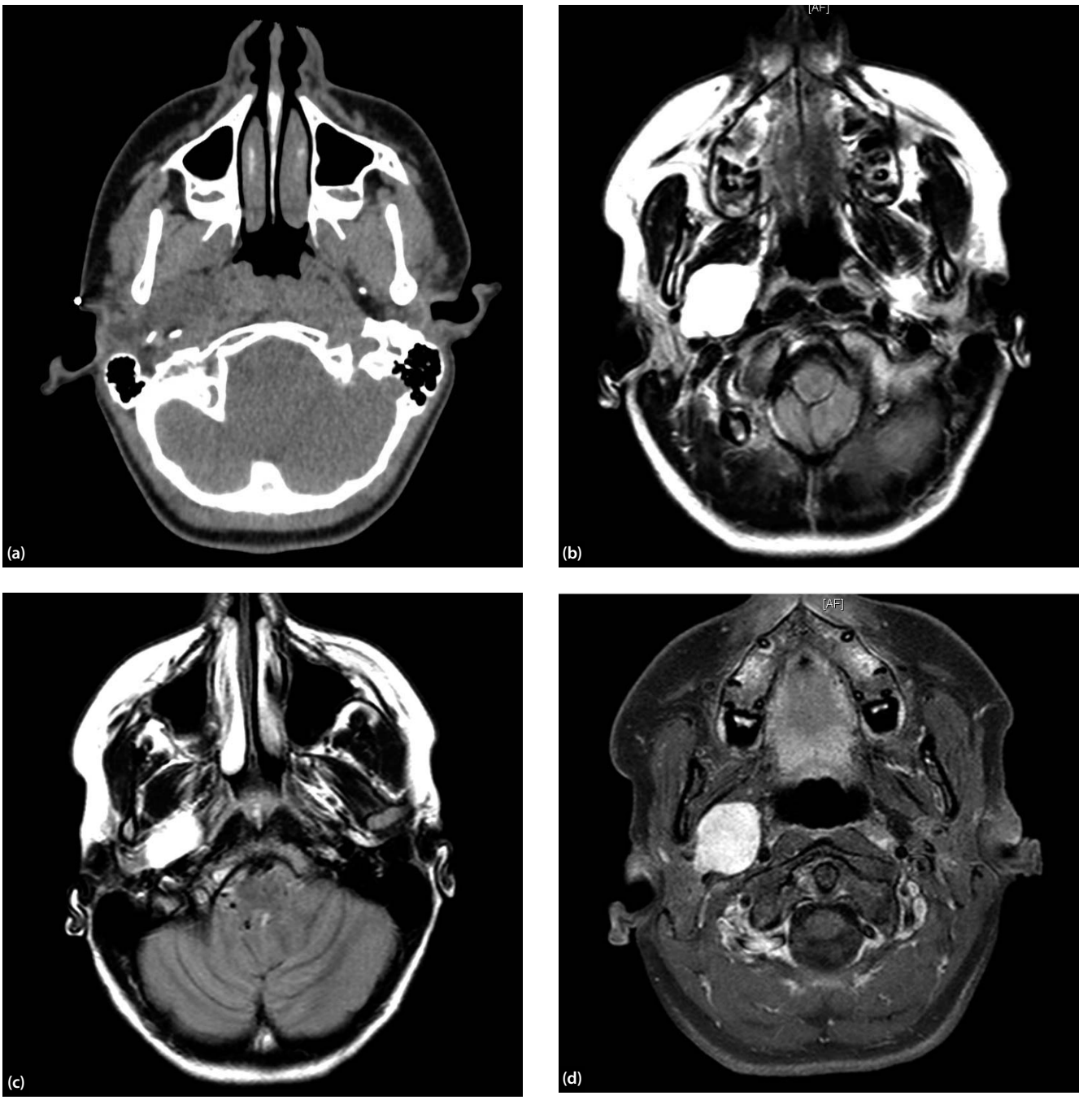

Figure 11.6 **(a)** Right parapharyngeal space tumour on CT shows the mass to be contiguous with the deep lobe parotid. **(b)** The same parapharyngeal tumour on MRI shows the mass to clearly arise from deep lobe of parotid. **(c)** Same right parapharyngeal space tumour on MRI showing limited involvement of deep lobe of parotid. These lesions are ideal for a transcervical – transparotid approach and may be suitable for a combined TORS resection with transparotid identification and protection of the facial nerve. **(d)** T1-weighted MRI with gadolinium and STIR sequence to suppress fat and demonstrate no fat plane in PPS between tumour and deep lobe of parotid.

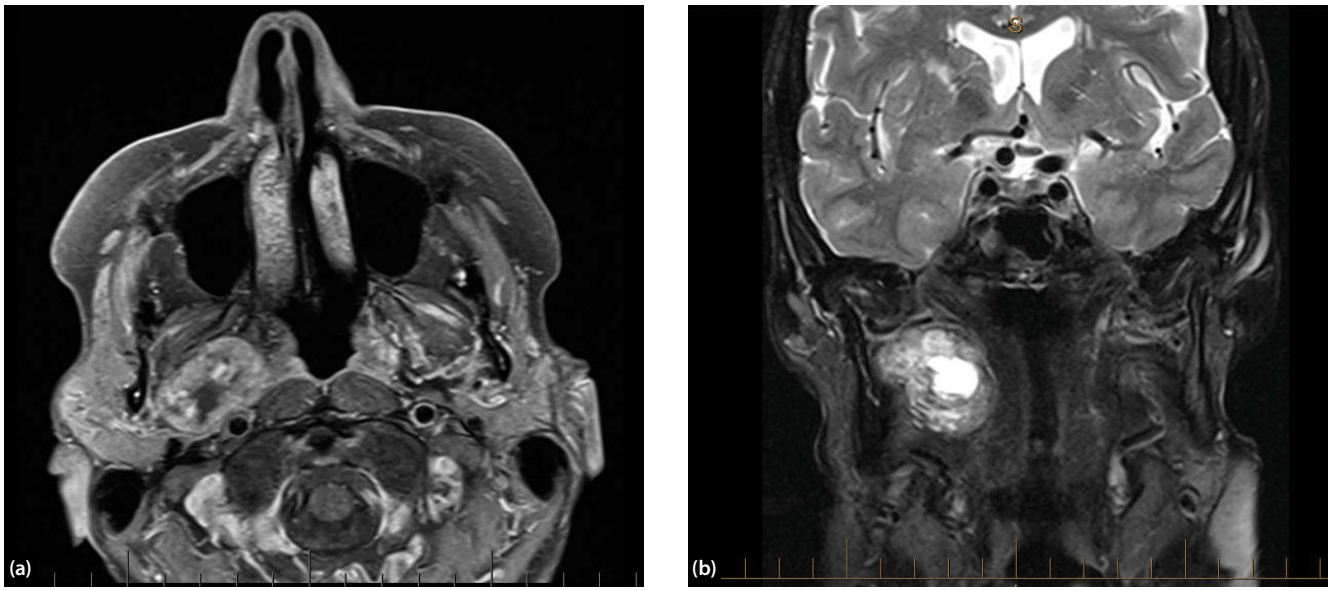

Figure 11.7 **(a)** MRI of right parapharyngeal space tumour. Lesion of the right parapharyngeal space with fat plane between tumour and deep lobe of parotid gland and rim of fat antero-medial to tumour. Lesion of the parapharyngeal space in the pre-styloid compartment displacing the carotid artery posteriorly. This variation is ideal for a TORS approach to resection. **(b)** Right parapharyngeal space tumour displacing carotid artery laterally. Favourable for TORS.

lesions with a thin uniformly smooth wall. On MRI, they appear as T1-weighted hypointense and T2-weighted hyperintense lesions with peripheral enhancement on post-contrast study. Schwannomas are fusiform, sharply circumscribed masses seen on CT as soft-tissue density masses with few cystic areas within. They show uniform enhancement on post-contrast study. On MRI, they appear heterogeneously hyperintense on T2-weighted images and isointense to hypointense on T1-weighted images. There are no flow voids within them which help to differentiate them from paraganglioma. The flow voids in paraganglioma give them the characteristic 'salt and pepper' appearance on MRI. Functioning paragangliomas may require further investigations including 24-hour urine screen for metanephrine.

Image guidance may be required to obtain a transcervical fine-needle aspiration biopsy for lesions not obvious or accessible in the oropharynx by a transoral approach.[15, 16]

Vascular lesions not amenable to resection may be considered for angiography and embolization. Angiography and embolization is also performed 24–48 hours before the excision of vascular tumours. In patients with lesions that encircle the internal carotid artery and who are at risk of trauma or resection of the internal carotid artery, balloon occlusion tests will need to be performed to assess the risk of neurovascular complications and assist in the decision-making process.

SURGICAL APPROACHES

Lesions of the parapharyngeal space are predominantly treated by surgery. In a systematic review of 1293 cases over a 25-year period, Kuet et al.[11] reported that 96% of patients had surgery. The aim of surgery is to remove the lesion with minimal morbidity. Adjuvant radiotherapy is reserved for malignant lesions or recurrent benign lesions with a high risk of recidivism. Chemotherapy is administered when indicated by specific histology such as rhabdomyosarcoma, positive margin status, tumour histology, perineural and lympho-vascular spread. Radiotherapy has also been used in patients who are considered a high surgical risk or for unresectable lesions. There are reports in the radiation literature of observational studies showing long-term control as defined by stable disease or limited regression in patients with paraganglioma undergoing radiation.[17, 18]

External transparotid, transcervical approaches to the parapharyngeal space have traditionally been considered the only safe access. The external approach was initially promoted in the 1950s mainly because of a poor understanding of the nature of these tumours and the surgical anatomical relationships. CT did not arrive until 1972 and was not in general use until 1979; the first MRI scanners arrived in the mid 1980s and were not in general use until the late 1990s. The improved imaging allowed consideration of approaches other than the traditional external approach.

In his treatise on parapharyngeal space surgery, Olsen[5] provides a clear description of the variety of external approaches. These include the transcervical approach which can be carried out in combination with a transparotid approach with or without a mandibulotomy for tumours that extend into the intratemporal fossa. Other combinations including orbitozygomatic, transmandibular and transpalatal approaches have been described. These approaches all involve wide exposure and a significant disruption of the normal anatomy of the

jaw and neck in order to facilitate safe resection of large or malignant neoplasms.

Transoral approaches, in the past, have generally been discredited. This is predominantly related to the risk to adjacent neurovascular structures, the risk of tumours spilled during resection, and the subsequent difficulty in dealing with recurrent tumour and finally the risk of infection from contamination of oral commensals. However, the advent of robotics and modern endoscopic systems have addressed many of these concerns for suitable tumours of the parapharyngeal space.

The choice of surgical technique is dependent on the tumour size, its relationship to the parotid gland and skull base and if the tumour is malignant.

Transcervical approach

The transcervical approach is the most commonly utilized approach, used in about 46% of cases (**Figure 11.8**).[11] It is ideal for small benign tumours independent of the deep lobe of the parotid gland. The procedure is performed under a general anaesthetic with the patient intubated with a nasotracheal tube. This allows an extra centimetre of anterior distraction of the mandible when accessing the parapharyngeal space. The patient is positioned with the neck extended and rotated opposite to the side of the lesion. The excision is performed through a transverse skin crease incision approximately 5 cm below the mandible to spare the marginal mandibular branch of the facial nerve. The platysma is divided and the superficial fascia of the submandibular gland is identified and raised with the superior flap to protect the facial nerve branches. The submandibular gland can be mobilized and displaced anteriorly to get greater access to the parapharyngeal space. The stylomandibular ligament is identified and divided and the mandible is distracted anteriorly. The parapharyngeal space is located between the digastric muscle and the periosteum of the

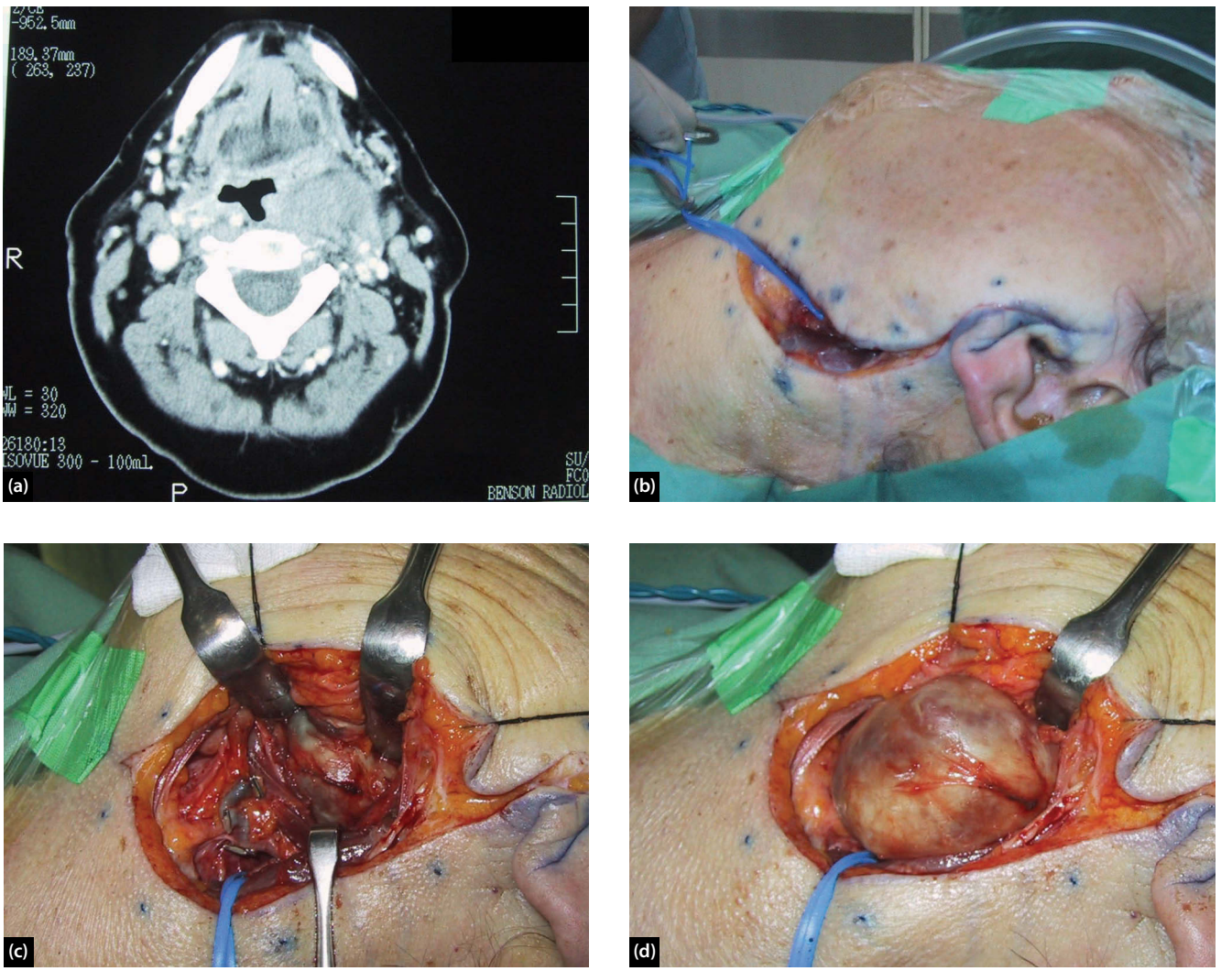

Figure 11.8 **(a)** Large left parapharyngeal space pleomorphic adenoma. **(b)** Large left parapharyngeal space pleomorphic adenoma – transcervical approach incision. **(c)** Large left parapharyngeal space pleomorphic adenoma – transcervical approach: following division of stylomandibular ligament and anterior distraction of mandible, dissection between digastric muscle and mandible provides access to the parapharyngeal space. **(d)** Large left parapharyngeal space pleomorphic adenoma – transcervical approach – delivery of tumour.

mandible and the medial pterygoid muscle insertion into the medial aspect of the mandible. The external carotid artery may need to be ligated to access and remove large tumours. Most of the dissection of the tumour is performed by blunt finger dissection staying close to the capsule of the tumour.

Transcervical – transparotid approach

This is the next most common approach, used in about 27% of cases (**Figure 11.9**).[11] This is well suited for lesions arising from the deep lobe of the parotid gland, for vascular tumours (as it allows access to vessels in the neck) and for the resection of malignant lesions. The operation is performed through a doubly modified Blair's incision as in a routine parotidectomy with a slight anterior extension of the cervical incision. The same procedure as described above for a transcervical excision is performed with an appropriate parotidectomy, identifying and defending the facial nerve.

Mandibulotomy

Transcervical and transcervical–transparotid approaches can be combined with a mandibular osteotomy. This was performed in about 9% of cases in the cumulative literature.[11] This allows access for excision of infiltrating malignancy and multifocal recurrent benign tumours and better visual access to the superior aspect of the parapharyngeal space and the skull base. Mandibulotomy can be performed in the standard paramedian position, or laterally with defence of the inferior alveolar nerve using an

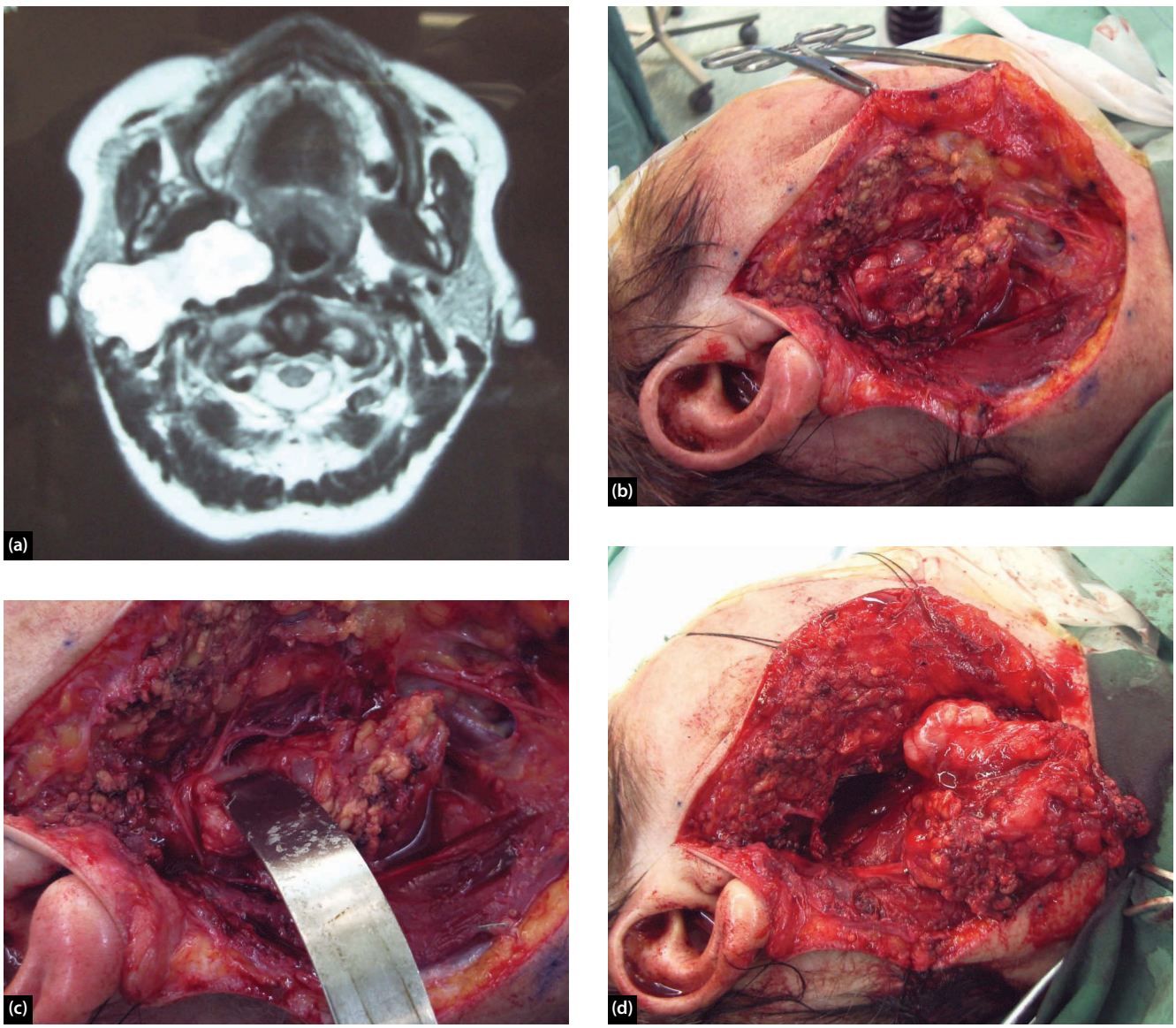

Figure 11.9 **(a)** Large right 'Dumbbell tumour' pleomorphic adenoma in parapharyngeal space. **(b)** Large right 'Dumbbell tumour' removal by transcervical and transparotid approach, superficial parotidectomy performed. **(c)** Large right 'Dumbbell tumour' removal by transcervical and transparotid approach, facial nerve being dissected from tumour. **(d)** Large right 'Dumbbell tumour' removal by transcervical and transparotid approach.

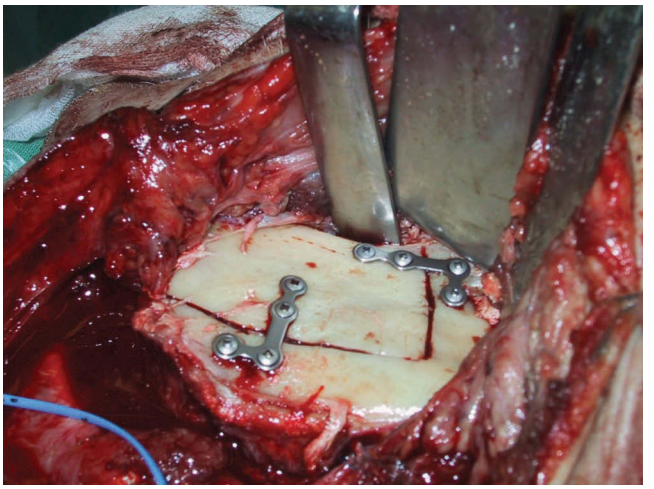

Figure 11.10 'Inverted L' osteotomy left mandible.

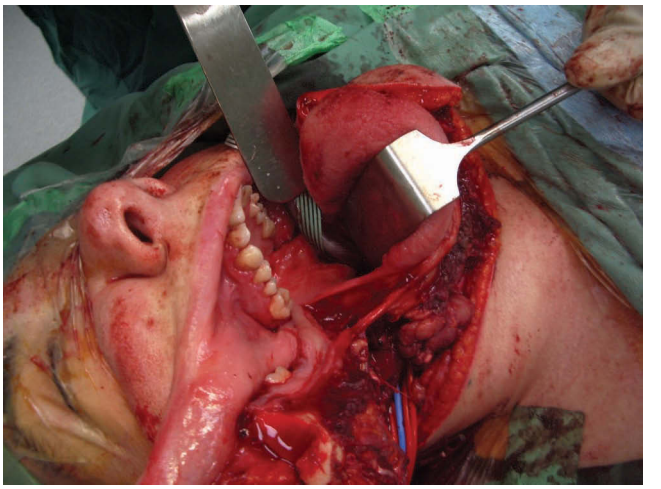

Figure 11.11 Transparotid, transcervical and transpalatal approach with paramedian mandibulotomy.

'inverted L' osteotomy[19] or by using a double osteotomy, above the lingula and in front of the mental foramen, again to protect the inferior alveolar nerve. Patients undergoing a mandibulotomy may require a tracheostomy, or may need to be intubated overnight to protect the airway. These patients may have a longer hospital stay, delay in return to normal nutrition and may be subject to complications such as temporomandibular joint dysfunction and malunion (**Figures 11.10** and **11.11**).

Transoral robotic surgery (TORS) of the parapharyngeal space: the paradigm shift (Figure 11.12a–c)

Embarking on TORS of the parapharyngeal space requires addressing the concerns and criticisms of this approach. The first issue is the risk to vital neurovascular structures. The traditional transcervical approaches are mooted as safer. However, in practice these approaches provide clear visualization of the lower cervical component of parapharyngeal space tumours and their relationship to the neurovascular bundle in the neck. The superior component is often difficult if not impossible to visualize. A true inspection of the relationship of tumour to neurovascular bundle would require wide access techniques such as mandibular osteotomy and/or infratemporal fossa approaches. As most tumours are benign salivary gland lesions, the superior aspect of the dissection is often performed with blunt finger dissection and inferior traction of the tumour to displace it off the neurovascular bundle.

The second issue is the risk of tumour spillage. Undertaking a TORS approach requires meticulous study of the imaging and at examination under anaesthesia, evaluating the mobility of the tumour and its lateral, superior and inferior relationships. The surgeon needs to understand the nature of the lesion, whether it is cystic, solid or mixed, whether it is benign or malignant, the thickness of its capsule and its relationship to the adjacent neurovascular structures.

The traditional support for external approach to the parapharyngeal space is based on a number of case series reports.[20–22] However, these are all retrospective, with a limited period of patient follow-up and with mixed pathological type including vascular tumours. These papers still report recurrence of benign tumours and tumour spillage. In practice, it is not uncommon during a standard transcervical approach for lesions to have their capsule disrupted. Sometimes when tumours are displaced inferiorly by pulling down on the tumour, a fragment of tumour may split off from the main mass of tumour. Careful inspection of the parapharyngeal space cavity with a telescope and irrigation of small fragments is required.

In contrast, there are a few papers reporting the results of a transoral approach.[23–25] There have been case reports of neural sheath tumours, neurofibromas, branchial cleft cyst tumours and benign mixed tumours being removed. Ducic et al. reported transoral resection of a series of benign tumours that displaced the carotid artery anteriorly.[24] Since the introduction of CT and MRI scans and a better understanding of the cross-sectional anatomy of the parapharyngeal space, there has been renewed interest in transoral resection of parapharyngeal space tumours.

The advantages of the da Vinci robotic surgical system have also renewed interest in transoral resection of parapharyngeal space tumours. The first reports of transoral robotic resection of parapharyngeal space by O'Malley et al.[28] described resection of a benign parapharyngeal space cyst without complications. The University of Pennsylvania's series reported ten patients, one of whom was converted to an open transcervical approach due to difficulty in finger dissection and to avoid tumour spillage.[29] Dehiscence of the mucosal incision was observed in two patients, none of the patients had residual or recurrent neoplasms at a follow-up on average 19.9 months. Their case series has reached 25 cases at the time of writing, with no recurrences and no patients requiring mandibulotomy or tracheostomy [personal communication]. Several authors have reported their experience with TORS for

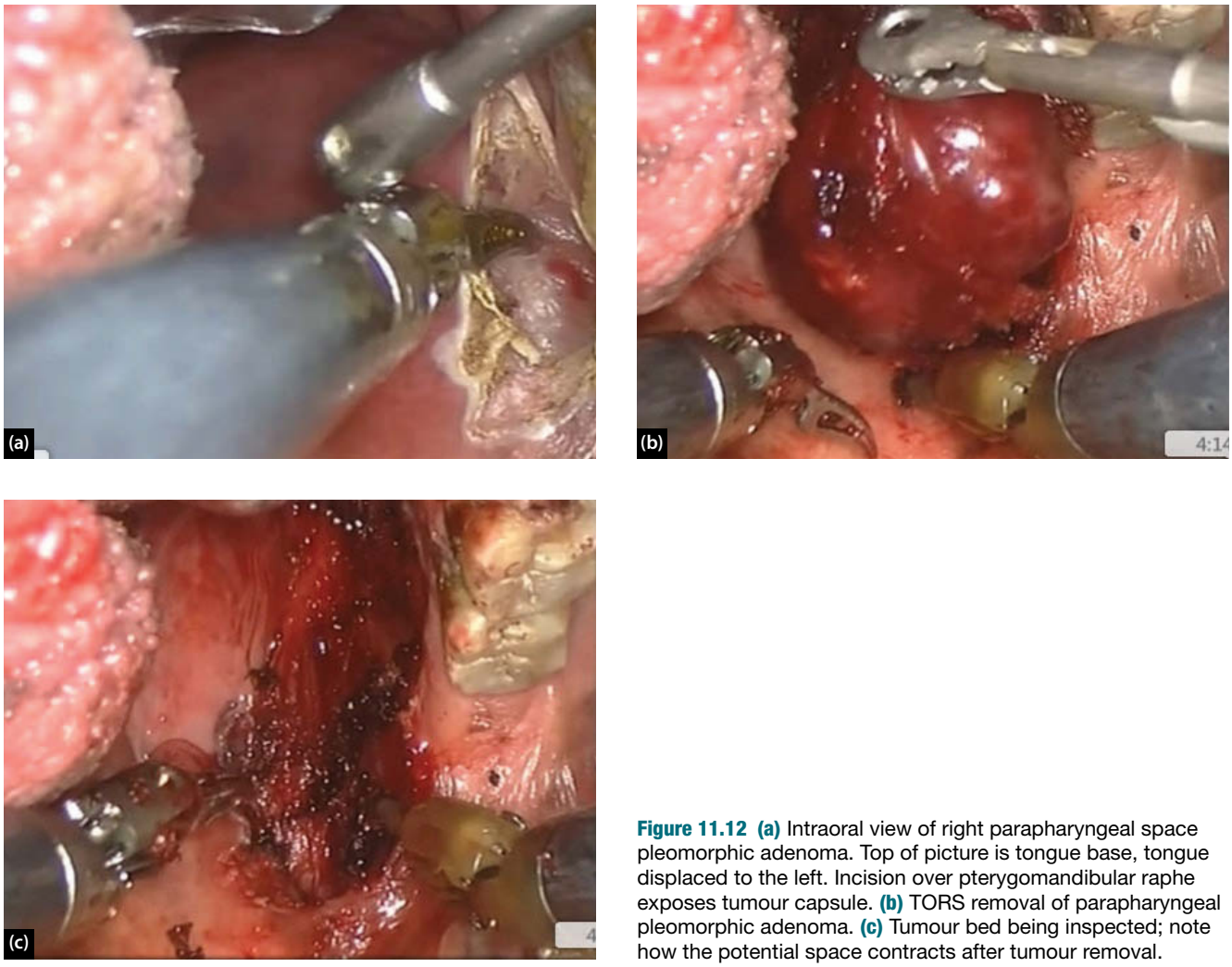

Figure 11.12 **(a)** Intraoral view of right parapharyngeal space pleomorphic adenoma. Top of picture is tongue base, tongue displaced to the left. Incision over pterygomandibular raphe exposes tumour capsule. **(b)** TORS removal of parapharyngeal pleomorphic adenoma. **(c)** Tumour bed being inspected; note how the potential space contracts after tumour removal.

parapharyngeal space tumour resection,[36–39] including a systematic review by Chan et al.[40]

Whereas the traditional transcervical approach allows the surgeon access to the inferior aspect of the tumour and a blind finger dissection at the superior aspect of the tumour, a transoral approach allows access to all aspects of the tumour. O'Malley et al. described combining the use of the robot to dissect the inferior and medial aspect of the tumour, with a blunt finger dissection to complete the superior and lateral dissection.[29] Patients at our institution are consented for a transoral robotic approach as well as for possible conversion to a transcervical approach with or without mandibulotomy if the transoral approach is not amenable to safe resection of tumour.

Cross-sectional imaging should distinguish vascular tumours and if necessary appropriate angiographic studies performed. The histological nature of tumours should be identified pre-operatively by fine-needle aspiration either by image control or by direct transcervical or transoral biopsy.

The transoral robotic technique has technical advantages, these being the three-dimensional high-resolution image with magnification, as well as the tremor filtration and motion scaling that allows delicate dissection. For those tumours with a thin capsule or with a significant cystic component, however, consideration must be given to other methods to control the spillage of tumours. This may include blunt finger dissection particularly of the superior and lateral aspects of the tumour, or decompression of the tumour medially by a controlled perforation of the capsule and using either a micro-debrider or coblator wand to evacuate the contents of the tumour within its cystic encasement before lateral dissection is proceeded with. It is important that the lateral aspect of the tumour is dissected bluntly and carefully to ensure that tumour rupture is kept to a minimum.

The transoral robotic approach does address some of the concerns previously leveraged against transoral approaches for parapharyngeal space lesions. The robot provides better visual access to the oral cavity, oropharynx and parapharyngeal space with excellent three-dimensional view with either 0-degree scope or a 30-degree scope which can be used to inspect the superior aspects of the parapharyngeal space up to the skull base, as well as be rotated to inspect the inferior extent of tumours of the parapharyngeal space. It has overcome the line-of-site limitations of the microscope and allows examination of the lateral aspects of the parapharyngeal space including

the stylomandibular tunnel. Scaled movement and tremor filtration also allows for dedicated dissection around the tumour capsule ensuring resection with a margin.

Pre-operative assessment and indication for transoral robotic surgery

The use of TORS for parapharyngeal space resection does require accurate pre-operative assessment. The focus of assessment is the relationship of the tumour to the carotid, tumour extent, tumour pathology and the nature of the tumour in terms of thickness of capsule and if the tumour is cystic or has cystic components. Fine-needle aspiration biopsy done either by image guidance or by transoral biopsy is required as benign and low-grade malignancies are considered suitable for TORS.

The ideal indications for TORS parapharyngeal space resection are benign salivary gland tumours occurring in the pre-styloid compartment, displacing the carotid artery posteriorly and laterally. These are the majority of parapharyngeal space tumours. Schwannomas and other benign neural tumours that are not deforming the carotid artery and not displacing the carotid artery medially are suitable for resection. Cystic lesions such as branchial cleft cysts are suitable for resection.

Relative indications include dumbbell tumours or tumours clearly arising in the parotid gland involving the deep lobe of the parotid gland. Such tumours with limited involvement of the deep lobe can be approached by a combined transcervical and transoral approach as described by Lee et al.[35] An absolute contraindication is tumour that is adherent or involving the carotid artery. Other contraindications include dumbbell tumours arising clearly from the parotid gland with significant involvement of the parotid gland (**Figure 11.13 a,b**), vascular tumours such as paragangliomas, tumours with bony involvement of the skull base, and malignant tumours.

POST-OPERATIVE CARE

All patients are managed in a High Dependency Unit (HDU) overnight for airway observation and for TORS patients, monitoring of potential oral bleeding that may compromise the airway. Patients are usually extubated after surgery with no personal experience or reports of post-operative airway compromise and no patient requiring prolonged intubation or tracheostomy. Patients having an external approach can usually commence an oral diet following surgery. Patients undergoing TORS are kept nil by mouth overnight and allowed clear fluids on the first post-operative day, free fluids on the second post-operative day and a soft diet progressing to a normal diet from the third post-operative day. Patients undergoing an external approach will have a drain *in situ* and when drainage subsides it is removed and the patient is discharged home. Subject to analgesic requirements patients are discharged on the second or third post-operative day.

COMPLICATIONS

The complications reported in surgery of the parapharyngeal space are related to vascular injury, lower cranial nerve injury, tumour spillage and recurrence and 'first bite syndrome'. Correct case selection and meticulous attention to pre-operative imaging with respect to tumour relationship to vessels should prevent risk of vascular injury

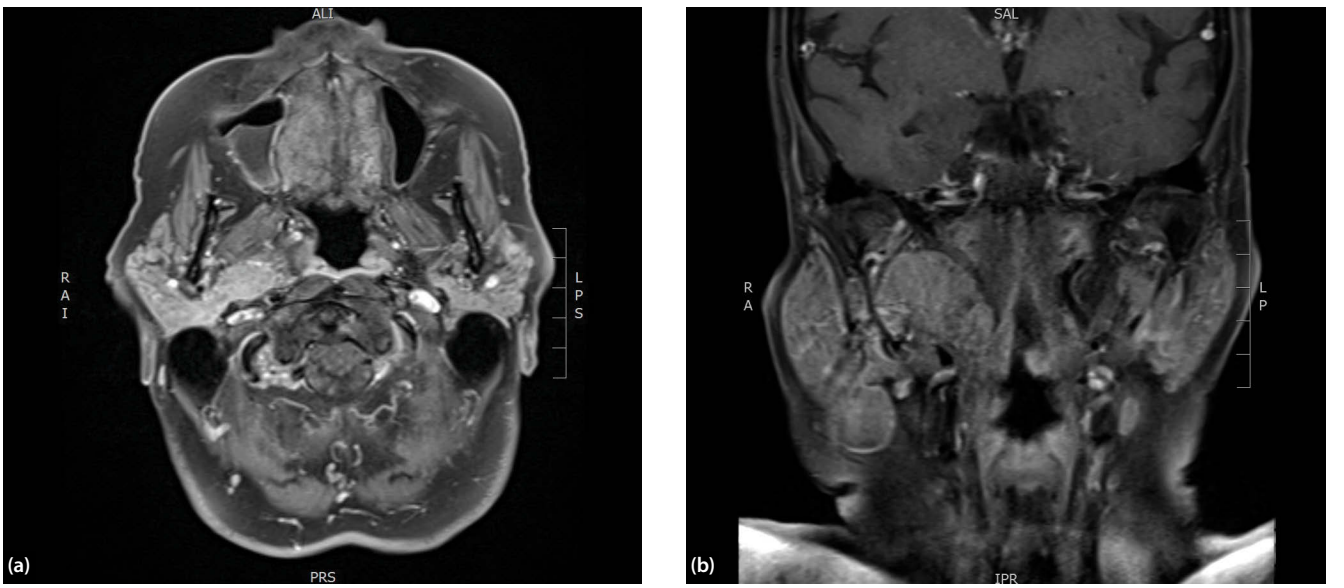

Figure 11.13 **(a)** Axial MRI showing 'Dumbbell' tumour extensively involving the parotid gland with extension through the stylo-hyoid tunnel into the parapharyngeal space. Such tumours are not suitable for TORS resection. **(b)** Coronal MRI showing 'Dumbbell' tumour extensively involving the parotid gland with extension through the stylo-hyoid tunnel into the parapharyngeal space.

including patients selected to undergo TORS for parapharyngeal space tumours. Neurogenic and malignant lesions are associated with greater risk to the facial, glossopharyngeal, vagal, accessory and hypoglossal nerves, with the vagus being the most common to be injured in about 13% of cases.[11] TORS avoids an external incision and avoids parotidectomy, with a reduced risk to the facial nerve and its branches.

It is unclear if tumour spillage will result in definite tumour recurrence. In the Mayo series reported by Hughes et al, tumour rupture was noted in 10 of the 68 cases performed by external approaches. This represents a spillage rate of 15% of pleomorphic adenomas; however, recurrence was only detected in one of those ten ruptured cases.[20] In series reporting experience with transoral resection techniques, Goodwin et al.[23] and Ducic et al.[24] report no tumour spillage seen during transoral resection. Tumuor spillage is not a common occurrence in carefully selected cases with thick capsules and no significant cystic components. In TORS parapharyngeal space tumour resection spillage appears not to be common or worse than with transcervical blunt dissection. The important things are to avoid sharp dissection against the tumour capsule and to use blunt dissection particularly at the lateral and superior and posterior aspects.

There is much debate but no consensus on the actions that need to be taken should the capsule be breached during dissection. The author's practice is to oversew the site of breach after suction drainage of any cystic fluid components within the tumour sac. The operative site should be generously irrigated with sterile water which is hypoosmolar and should promote tumour cell lysis. The role of post-operative radiotherapy is unclear particularly as evidence suggests low rates of recurrence of tumour, despite tumour spillage.[20] The author recommends radiotherapy for large uncontrolled spills with an inability to confirm complete clearance of spilt tumour and for patients undergoing surgery for recurrence with significant risk of facial nerve injury should subsequent surgery be required.

Bleeding can be avoided by meticulous haemostasis using haemoclips and the use of tissue haemostatic agents. Trismus may be present in the early post-operative period but is not a long-term complication, often resolving within 2 weeks of surgery. The other complication reported in external approach surgery is first bite syndrome. As discussed by Chiu et al,[41] it has been theorized to be related to the loss of sympathetic supply to the parotid gland with subsequent increased sensitivity of the myoepithelial cells to parasympathetic innervation. This syndrome has not been reported in transoral resection and is seen as a distinct advantage of transoral resection over external resection.

FUTURE RESEARCH

- More complicated and extended approaches may be required for malignant and complicated tumours involving the carotid artery or extending out of the parapharyngeal space.
- Radiotherapy may have a primary role for high-risk patients unable to have surgery or for select benign vascular lesions where surgery may contribute to significant morbidity from injury to multiple lower cranial nerves.
- Radiotherapy and chemotherapy may have an adjuvant role in some malignant tumours of the parapharyngeal space.
- TORS for parapharyngeal space tumours has advantages for the true pre-styloid benign salivary gland tumour, which is the most common tumour in this space. Its use in other tumours of this space is expanding with better understanding of tumour relationships to vital neurovasculature structures through improved imaging.
- The advent of image guidance and real-time imaging may further enhance the cause of transoral surgery.
- Improvements in robotic instruments, particularly the imminent arrival of single port instruments, will improve access and precision of dissection.
- The introduction of haptic feedback in robotic surgery may contribute to reducing the risk of capsular rupture and tumour spillage.

KEY POINTS

- Parapharyngeal space tumours are a rare subset of head and neck tumours.
- The majority are benign and treated by surgical excision.
- Evaluation of these lesions needs to be meticulous. The use of multiplanar imaging with CT scans with contrast and MRI scans with fat suppression and gadolinium for contrast, when appropriate, can provide accurate details of the nature of the lesion and where it has arisen from.
- Image-guided fine-needle aspiration cytology assists with histologic diagnosis.
- Together, this information helps with planning management of these tumours.
- Some benign vascular and neurogenic tumours are best observed by serial MRI scans, if there is significant risk of debilitating multiple lower cranial nerve palsies from surgery.
- Surgical approaches have to be carefully planned and may include the transcervical approach which can be carried out in combination with a transparotid approach with or without a mandibulotomy.

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CHAPTER 12

ORAL CAVITY TUMOURS INCLUDING LIP RECONSTRUCTION

Tim Martin and Omar A. Ahmed

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SEARCH STRATEGY

Data in this chapter may be updated by a MedLine search using the following keywords: oral cancer mouth cancer, squamous cell carcinoma, neck metastases, tongue cancer and lip cancer.

ORAL CAVITY TUMOURS

Tim Martin

INTRODUCTION

The oral cavity is the uppermost part of the digestive tract. The oral cavity starts at the mucocutaneous junction of the lips (the vermilion border) extending posteriorly to the junction of the hard and soft palate superiorly, anterior fauces laterally and the junction of the anterior two-thirds and posterior third of the tongue inferiorly. Neoplasms of the oral cavity may be classified topographically using the International Classification of Diseases for Oncology,[1] neoplasms of the oral cavity being coded C00–C06 depending on site of tumour (C01 – base of tongue, C05.1 – soft palate and C05.2 – uvula are excluded from this chapter since they form part of the oropharynx).[1]

The oral cavity is lined by stratified squamous epithelium of varying degrees of keratinization. Primary tumours of the oral cavity may be derived from the mucosa, salivary glands, neurovascular tissues, bone or dental tissues. Over 90% of tumours of the oral cavity are squamous cell carcinomas. Globally over 300,000 people are diagnosed with oral cancer each year, it being the eighth most common malignancy.[2] There is considerable geographic variation, the incidence of oral cancer being particularly high in South-East Asia and some Eastern European countries. The incidence of oral cancer in males in England approximates 6 per 100,000 per annum compared to 4 per 100,000 per annum for females. The age-standardized rate for oral cancer in Melanesia is as high as 25 per 100,000 per annum (**Figure 12.1**).

The registration rate for oral cancer has risen by over 20% in the last 30 years in England and Wales, particularly in those under 65 years of age.[3, 4] The increasing incidence of HPV associated oropharyngeal carcinoma may contribute to the reported increase in oral cancer in those publications which do not differentiate between oral cancer and oropharyngeal cancer, however the increase in oral cancer incidence is confirmed in studies specifically isolating the oral cavity site.[5] The author has seen a 10% increase in incidence and 20% increase in prevalence of oral cancer in his own practice between 2000 and 2010, cancers of the oral cavity not being associated with HPV. The increasing incidence of oral cancer has been noted

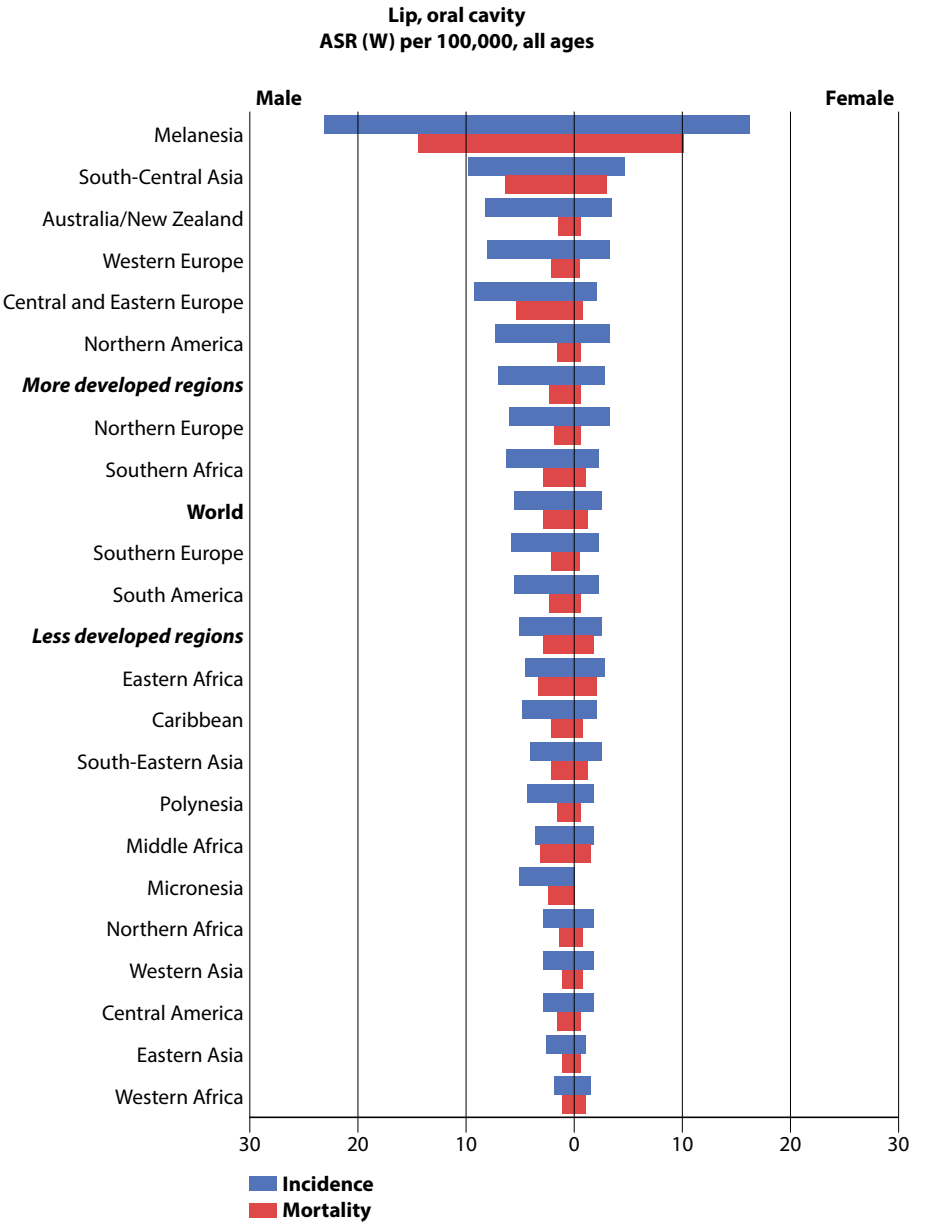


Figure 12.1 Estimated age-standarized rates (World) per 100 000 of lip and oral cavity cancer (Source: GLOBOCAN 2012, http://globocan.fr)

in other populations[6] and may be as a consequence of increasing alcohol consumption. A comprehensive review of international trends in head and neck cancer highlights concerns regarding alcohol consumption.[7] Oral cancer is more common in males, who usually present in the 6th and 7th decade although the incidence of oral cancer in young people seems to be increasing.[8,9] Tobacco and alcohol consumption are the major aetiological factors in the development of oral cancer,[10] oral cancer being considered largely preventable.

If oral cancer is detected when it is confined to the oral mucosa 5-year survival rates exceed 80%, decreasing to 40% for those with regional disease at presentation and 20% if distant metastasis has occurred. Early oral cancer is associated with an improved prognosis and less extensive treatment in attempt to cure the patient. A significant number of patients continue to present with advanced disease and improved public awareness of symptoms associated with oral cancer is a potential solution to this problem.[11,12] Research is required regarding selected or opportunistic screening for oral cancer, but at present there is insufficient evidence to support screening.[13]

The management of patients with oral cancer requires a concentration of medical expertise and resources. For the patient to receive optimal management a truly multidisciplinary approach is required.

WORKUP OF PATIENTS

History

The workup of a patient with suspected oral cancer starts with a detailed accurate history. The patient's symptoms should be documented and a thorough history of each symptom clarified. A short systematic review should be

included, asking specifically for symptoms suggestive of metastatic disease or synchronous aerodigestive tract tumour.

The patient's medical history including medications and allergies should be recorded. A frequently neglected aspect of history taking is the patient's social history. Patients with oral cancer are likely to face the prospect of major surgery, radiotherapy or chemoradiotherapy. The social circumstances of a patient will significantly influence management decisions. Support packages instituted early in the patient's management may help with timely delivery of care and increased patient compliance. If it is anticipated that free-flap reconstruction may form part of the treatment plan then direct questions regarding proposed donor sites should be asked such as hand dominance, intermittent claudication or chronic chest disease.

Examination

While taking a history from a patient the clinician should make note of such things as the patient's mobility when they enter the room, the patients affect, dysarthria or clues to smoking and drinking habits.

The formal examination should ideally be conducted in a dental chair with good lighting. The neck should be systematically palpated for cervical lymphadenopathy, although imaging of the neck in all patients with suspected oral malignancy should be conducted. Using two dental mirrors to help with retraction and visualization, the oral cavity and oropharynx should be examined in their entirety in a systematic manner. All patients should undergo flexible endoscopic assessment of the upper aerodigestive tract mucosa if there is a high index of suspicion for oral cancer. A dental examination should form part of the initial consultation so that dental treatment may be started early in anticipation of surgery or radiotherapy.

Occasionally pain or trismus may limit the examination and in these circumstances an examination under anaesthetic (EUA) should conducted. A restorative dental opinion should be sought before EUA so that necessary dental extractions can be conducted at the same time.

Investigations

Investigations conducted at the initial consultation will depend on the clinician's suspicion that the patient may have oral cancer. Simple investigations that may be conducted at the first appointment include:

- photographs
- incisional biopsy of mucosal lesions
- fine-needle aspiration cytology of suspicious lymphadenopathy
- orthopantomogram
- chest X-ray – if chest CT is not anticipated
- electrocardiogram
- routine bloods – full blood count, urea and electrolytes, liver function tests and clotting.

Biopsy should always be conducted prior to definitive treatment, preferably by a senior member of the team. The timing of a biopsy in relation to other investigations should be carefully considered. If the patient presents with a large tumour where therapeutic or elective management of the neck is anticipated based on primary tumour characteristics, then a biopsy may be safely conducted prior to imaging. If the patient presents with a suspicious small lesion then it is judicious to conduct imaging prior to biopsy to minimize local oedema at the biopsy site or local reactive lymphadenitis, thus upstaging the disease on imaging. Small alveolar tumours should be imaged prior to biopsy since increased marrow signal secondary to inflammation associated with a biopsy may commit the patient to a segmental resection. The biopsy site should be at the periphery of the lesion to include a sample of normal mucosa. A large, deep biopsy may give information regarding depth of invasion and hence the potential necessity to conduct a neck dissection. It has been demonstrated that if tumour thickness on biopsy is >2 mm then the final tumour thickness is usually greater than 3.5 mm,[14] suggesting an elective neck dissection (END) may need to be considered. Unfavourable tumour factors such as perineural spread, vascular permeation and a non-cohesive invasive front are indicators to the probability of positive margins and long-term prognosis. Unfavourable features may lead one to consider wider surgical margins where feasible to reduce local recurrence (accepting that these same features suggest a poorer long-term prognosis) while balancing the quality-of-life issues raised by conducting such a resection.

Once oral malignancy is confirmed histologically additional investigations may be conducted relating to:

STAGING OF THE DISEASE

- CT +/– CT chest
- MRI
- USS (of the neck or primary) +/– USS guided FNA of suspicious lymphadenopathy
- PET.

There has been much debate regarding the extent to which an individual should be screened for second aerodigestive tract tumours or metastatic disease. To subject a patient to major head and neck surgery and an extended hospital stay is clearly inappropriate in the presence of established distant disease, however, extensive surgery may be an excellent mode of palliation. Currently screening for distant metastases is indicated in patients with multiple cervical nodes, recurrence, second primary,[15] or advanced disease.[16] The modality of choice for screening is a CT chest, although ^{18}FDG-PET may have an increasing role.[15] The routine use of panendoscopy in the workup of the patient with oral cancer is not necessarily warranted,[17] although targeted panendoscopy in smokers may reveal synchronous neoplasms in up to 10% of patients.[18] Once the patient has had appropriate investigations the tumour may be staged using the TNM system.[19]

TNM staging

The staging of head and neck cancer will be dealt with in detail in Chapter 4, Staging of head and neck cancer. However, it is worth highlighting recent changes to the TNM staging recommendations published in the American Joint Committee on Cancer (AJCC) 8th Edition Cancer Staging Manual[20] and the Union for International Cancer Control (UICC)[21] which are of particular importance to the staging of oral cavity cancer (OCC). The changes and the rationale behind them are reviewed in detail in Lydiatt et al.[22]

T stage

1. A T0 category is no longer assigned to p16 – OPSCC and other non-HRHPV cancers e.g. larynx, oral cavity and hypopharynx as an exact primary site is, by definition, unable to be established and therefore cannot be assigned to a specific anatomical sub-site.
2. TNM 7th Edition incorporated tumour thickness into the TNM staging criteria as previous data had demonstrated that tumour thickness had prognostic value.[23] However, in TNM 8th Edition tumour thickness has been replaced by an assessment or measurement of tumour depth of invasion (DOI) as this has been shown to be a better prognosticator that tumour thickness.[24]
3. Three DOI groups have been defined: ≤ 5 mm, > 5 mm but ≤ 10 mm and > 10 mm. Each incremental increase in DOI results in an increase in clinical T stage (cT) and pathological T stage (pT) levels.
4. cT DOI relies on clinical examination and measured radiological evidence whilst pT is measured by a perpendicular dropped from a line drawn at the level of the basement membrane (See **Figure 12.1**).[22]
5. These modifications have led to the following revised T stages
   a. **T1:** ≤ 2 cm, ≤ 5 mm DOI
   b. **T2:** ≤ 2 cm, DOI > 5 mm and ≤ 10 mm or > 2 cm but ≤ 4 cm, and ≤ 10 mm DOI
   c. **T3:** > 4 cm or any tumour > 10 mm DOI
6. In addition, 'extrinsic muscle infiltration' is no longer a staging criterion for T4 stage as it has been replaced by DOI.

N stage

1. Extra-nodal extension (ENE) has been added as a prognostic variable in addition to the number and size of metastatic lymph nodes.
2. Radiological evidence alone is insufficient to determine ENE and must be associated with overt clinical evidence of invasion of adjacent anatomical structures (e.g. overlying skin or adjacent nerve).
3. Pathological determination of ENE is subdivided into minor ENE, when ENE < 2 mm beyond the lymph node capsule and major ENE when extension is > 2 mm beyond the capsule +/– soft tissue metastatic deposits are evident. This minor/major distinction is for data collection purpose at this stage and currently, either subdivision is considered ENE positive.

PLANNING OF RECONSTRUCTION

The most appropriate reconstruction will be determined by multiple factors, notably characteristics of the primary site and the anticipated defect, the medical and social history of the patient and potential donor site characteristics. The reconstructive surgeon should have the ability to raise or harvest many different types of local, regional or distant flaps when dealing with head and neck malignancy. For complex bony reconstructions, computer aided planning is invaluable in achieving an optimal cosmetic and functional outcome (**Figure 12.2**).

Focused examination or investigations regarding proposed reconstruction include:

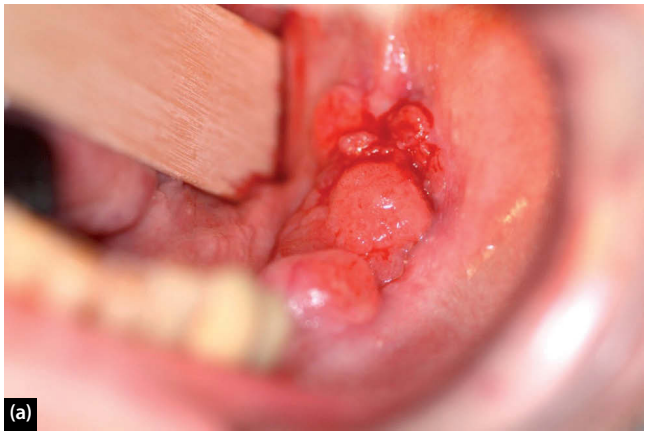
- Allen's test of the vascular supply to the hand if a radial free forearm flap is anticipated
- MRA / angiography of the leg vessels if composite fibula reconstruction is anticipated
- thorough examination of the chest and abdomen if a deep circumflex iliac artery (DCIA) free flap is anticipated
- CAD / CAM models if complex composite reconstruction is anticipated
- dental impressions for all maxillary tumours.

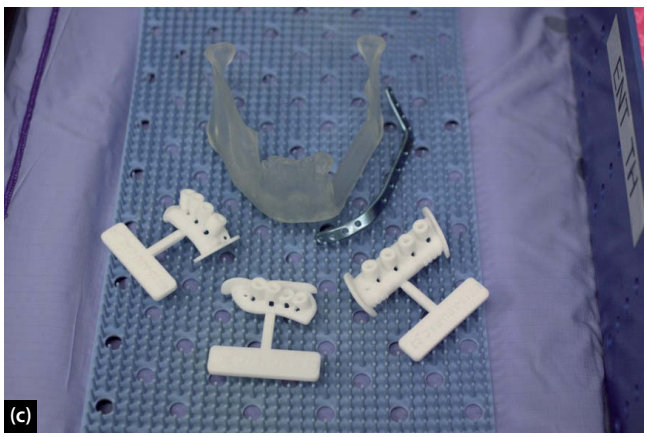
Anaesthetic assessment

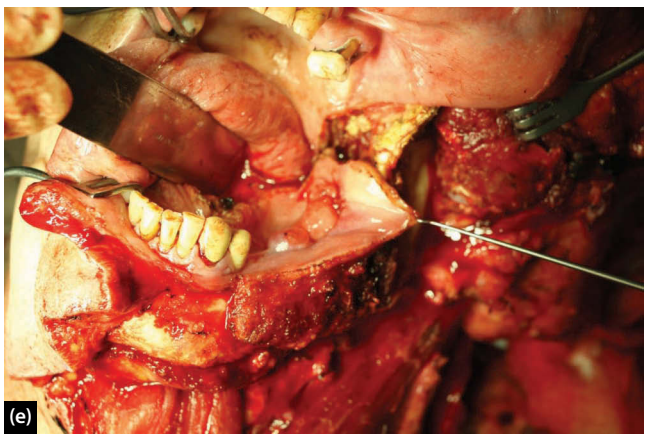
It is advisable to liaise with the anaesthetist early in the treatment planning of the patient, especially where a difficult airway is anticipated.

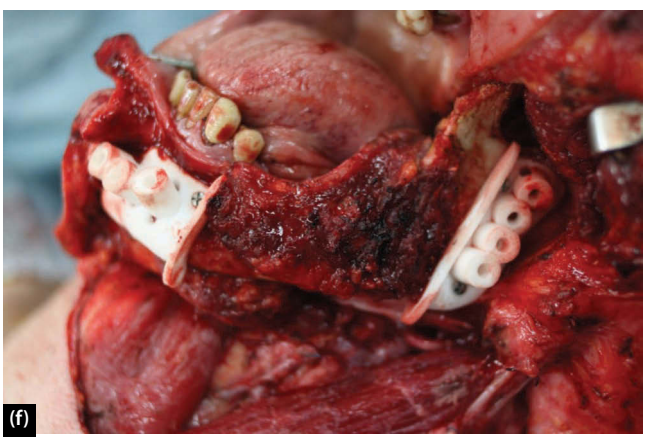
The patient should be seen by the dietician early in their management for dietary advice. Consideration should be given to a percutaneous endoscopic gastrostomy (PEG) to facilitate feeding,[25] however insertion of a PEG is not without morbidity and quality of life issues.[25, 27] A preoperative scoring system has been developed to facilitate decision-making regarding enteral feeding support.[28] Nasogastric feeding may be more appropriate if complex surgery is not anticipated and post-operative radiotherapy (PORT) is unlikely. It is beneficial if the patient meets the speech and language therapist and counsellor prior to starting definitive treatment.

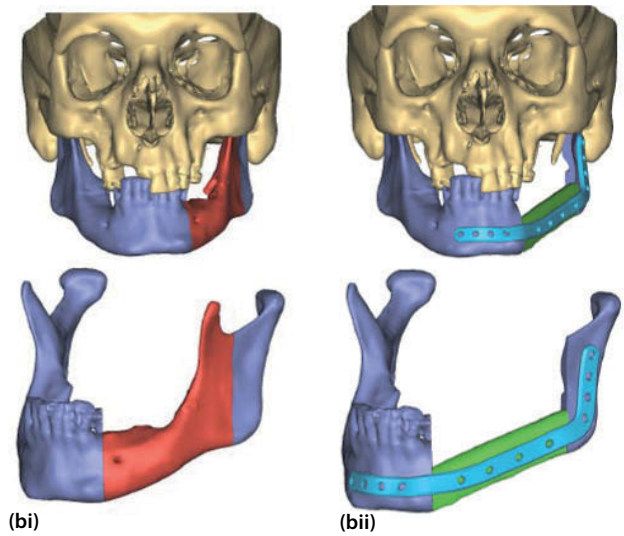
Once the patient has been thoroughly worked up a discussion should occur with the whole Head and Neck team to formulate an appropriate treatment plan. The proposed treatment should then be discussed with the patient and informed consent gained. Informed consent should be tailored to the individual and results achieved in the operating unit. The general success rate of microvascular free-flap surgery is greater than 95%, however 5–15% of patients may require return to theatre for complications such as flap compromise, haematoma or infection. It should be remembered that the peri-operative mortality rate for major head and neck surgery is 1–3%. Patient's age alone should not rule out major surgery and microvascular reconstruction,[29] it being the patient's co-morbidity that primarily influences the incidence of post-operative complications[30, 31] and prognosis.[32] The benefit of major microvascular surgery in patients with significant comorbidity (e.g, an Adult Comorbidity Evaluation Index 27 of Grade 3), should be carefully considered.

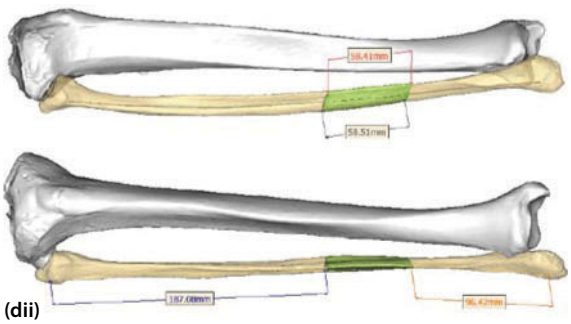












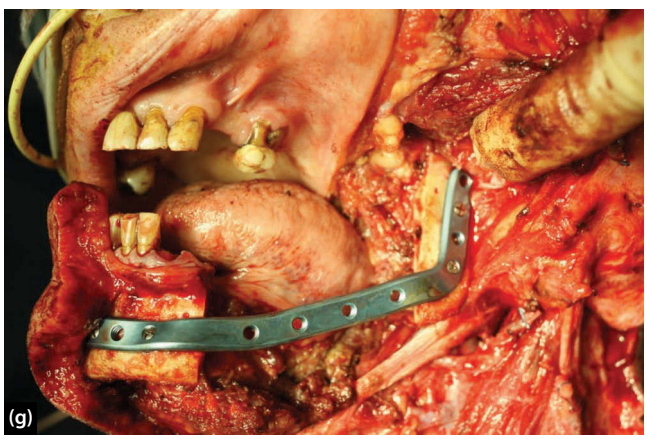


Figure 12.2 **(a)** The primary is a left retromolar trigone ulcer staged T4a, and histologically a squamous cell cancer in a 66-year old male. **(b)** The intended amount of mandible resection is shown in red with the planned donor bone from the fibula in green. Note custom-made pre-bent reconstruction plate. **(c)** Custom-made cutting guides, patient specific implants are 3D printed prior to the operation. **(d)** Computer-aided surgical planning allows 3D printing of cutting guides for the fibula **(e)** Tumour exposed prior to resection. **(f)** Mandible cutting guides in position prior to osteotomy. **(g)** Pre-bent plates anchored in place prior to bony flap inset. *(Continued)*

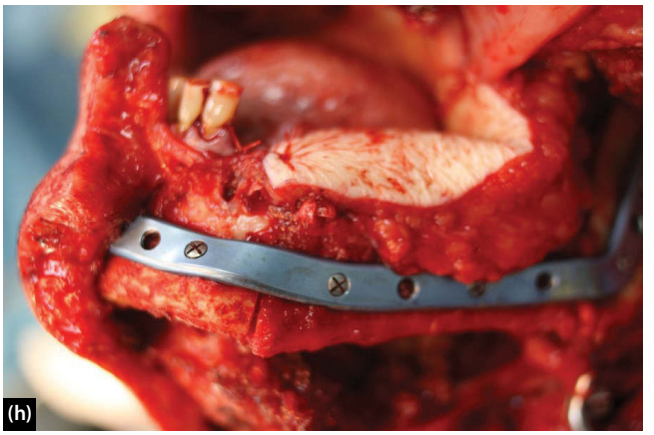


Figure 12.2 (Continued) (h) Donor fibula fixed into the defect using the pre-drilled holes. Note soft-tissue component of the free flap to line the oral cavity. Figures courtesy of Mr James Adams, Newcastle upon Tyne.

SURGICAL ACCESS

The ultimate aim of surgical resection is removal of the tumour with adequate margins. For the majority of oral tumours this may be achieved via a per oral route[33] with good retraction and lighting. Patients with trismus, microstomia, large or posteriorly based oral tumours may require additional access procedures to ensure adequate clearance of the tumour. The role of transoral robotic surgery continues to expand and undoubtedly its application to posterior oral tumours will develop in those institutions able to invest in this technology.

Mandibulotomy

Bone resection is no longer an acceptable method of improving access to oral tumours. A mandibulotomy gives good access to large or posteriorly located tumours. An orthopantomogram (OPG) radiograph is required prior to conducting this procedure to demonstrate the dental anatomy of the area (**Figure 12.3**). Typically, the procedure is accompanied with a lip split. Mandibulotomy without a lip split has been described to minimize facial scars,[34] however access is not as great as when a lip split is conducted. It has been demonstrated that patients have minimal concerns regarding the scar associated with a lip split mandibulotomy.[35]

The neck dissection incision is extended anteriorly to split the lip. Multiple incision designs have been proposed for the lip split.[36] An incision around the chin prominence tends to make the prominence more pronounced, a vertical incision over the chin point producing a more cosmetic result (**Figure 12.4**). Incorporation of a chevron between the chin prominence and vermilion aids closure and breaks up the scar. The intended incision should be marked and temporary tattoos created with needle and ink at the vermilion to ensure accurate reapproximation at the end of the procedure.

The osteotomy should be conducted anterior to the mental foramen to preserve labial sensation. The preferred site for the osteotomy is the paramedian area (between the lateral incisor and canine) since the distance between the tooth roots is greater,[37] dental complications consequently being less than median osteotomies.[38] An osteotomy in the paramedian area preserves the attachments of geniohyoid, genioglossus and digastric to the major segment, only mylohyoid requiring division to mobilize the minor segment. If the distance between the lateral incisor and canine roots is insufficient to accept a saw blade then the lateral incisor should be removed and the osteotomy conducted through the socket to minimize the possibility of osteoradionecrosis should a tooth be damaged. Once the site of osteotomy is established miniplates are adapted and applied to the mandible bridging the proposed osteotomy site. The plates are then removed and the osteotomy conducted using a fine reciprocating saw blade.[39] Application of plates prior to osteotomy ensures maintenance of occlusion at the end of the procedure, although a discontinuity the width of the cutting saw is created. A modified mandibulotomy where only the buccal cortex is cut with a saw, the lingual plate being fractured with a small osteotome, has been described so ensuring bone-to-bone contact at the end of the procedure and may lead to better osseous healing.[40] The mandible and cheek flap may now be retracted laterally and superiorly giving excellent access to the posterior oral cavity and oropharynx.

The non-anatomical position adopted by the temperomandibular joint (TMJ) during this procedure does not give rise to long-term TMJ dysfunction.[41]

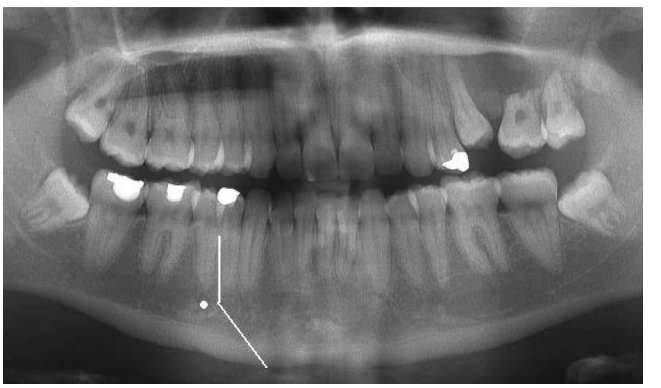


Figure 12.3 OPG showing surgical planning for a planned osteotomy. Figure courtesy of Mr Matt Kennedy, Newcastle upon Tyne.

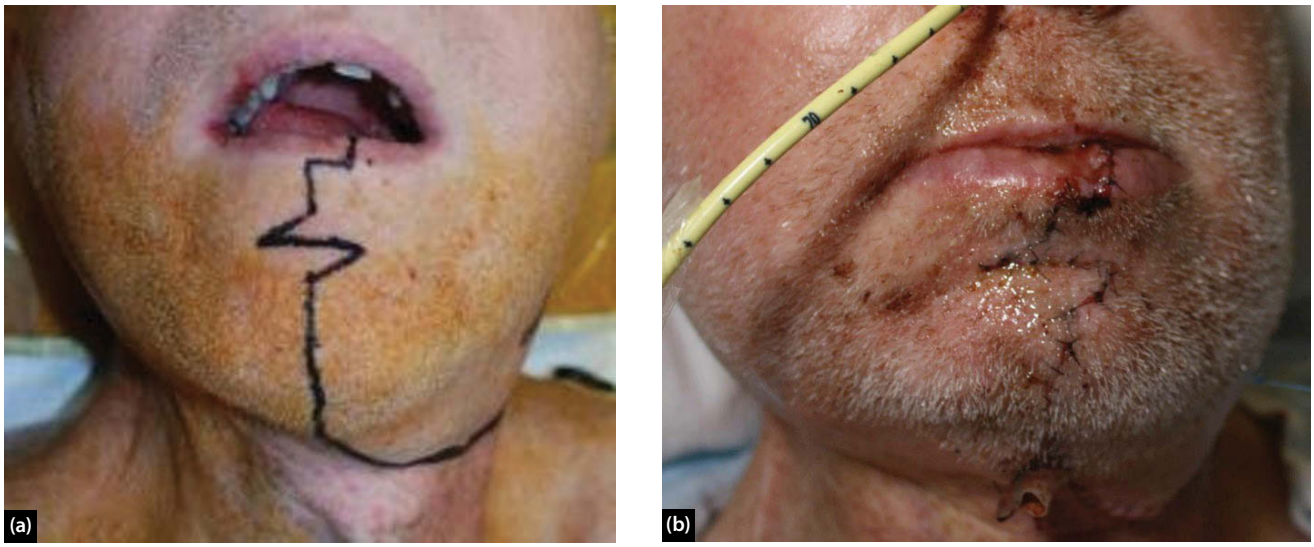


Figure 12.4 Suggested lip split incision that avoids the incision extending around the chin prominence. Figure courtesy of Mr Matt Kennedy, Newcastle upon Tyne.

Visor approach and lingual release

This approach is generally reserved for when bilateral neck dissections are performed. The visor approach may also be appropriate for recurrence or second primary tumours in patients who have received previous radiotherapy to the mandible. The visor approach avoids facial incisions, the incision being located in a cervical skin crease. A mastoid to mastoid visor flap is elevated in the subplatysmal plane to the lower border of the mandible. An intraoral mucosal incision is made in the lingual gingival sulcus from the posterior molar on one side to the posterior molar of the other. In edentulous patients the incision is made on the alveolar crest. The mylohyoid, geniohyoid, genioglossus and digastric muscles are detached from the lingual aspect of the mandible allowing the floor of mouth and tongue to be dropped into the neck. Care should be taken to ensure the lingual and hypoglossal nerves are not injured during the dissection. The reattachment of geniohyoid and genioglossus muscles at the end of the procedure is important to reconstitute the floor of the mouth. This may be facilitated by drilling holes in the lower border of the mandible through which securing sutures are passed. Alternatively, genial muscle reattachment may be facilitated by conducting a small box osteotomy of the lower border of mandible incorporating the muscle attachments and relocating at the end of the procedure with wires or miniplates.

Excellent access may be achieved without the necessity of a lip split, however the expected gain in cosmesis has not been proven and this technique is associated with significantly greater functional deficit post-operatively[41] compared to lip split and mandibulotomy.

Upper cheek flap

The upper cheek flap may be required to augment access to large or posterior maxillary tumours. The cornea of the eye should be protected in all patients. Anterior tumours requiring improved access may be approached via a modified Weber–Ferguson incision without extension. The modified Weber–Ferguson approach is essentially an upper lip split extending into a lateral rhinotomy incision. It is imperative that the incision be marked out accurately and temporary localizing tattoos created prior to starting the procedure. The lip split is usually conducted along the ipsilateral philtral column to the base of the columella. The incision extends laterally along the floor of the nose then follows the alar crease to its superomedial end before continuing to a point 6–8 mm medial to the medial canthus. Locating the vertical limb of the incision on the nose rather than cheek respects the concept of aesthetic facial units and gives a superior aesthetic outcome. The incisions are deepened to bone and the cheek flap raised in the subperiosteal plane, preserving the infraorbital nerve unless it is to be sacrificed on oncological grounds. Elevation of the flap requires a mucosal incision in the gingivo-labial and gingivo-buccal sulcus to a point where the flap incision merges with the resection margins of the tumour. Greater access is afforded by extending the modified Weber–Ferguson incision either with a subciliary incision (Diffenbach extension) or medial canthal incision (Lynch extension). An infraorbital orbitotomy may facilitate access[42] but is not usually required for tumours confined to the oral cavity.

SURGICAL MARGINS

The ultimate aim of surgical resection is adequate clearance of the tumour. Inadequate clearance of tumour results in increased local recurrence and decreased long term prognosis.[43, 44]

Indications for PORT include positive or close margins. However, local recurrence rates following PORT do not approach those in whom adequate clearance is achieved at the primary operation.[44, 45]

Increasing resection margins in the region of the head and neck potentially results in increased functional and cosmetic deficit. Resection margins of up to 2 cm have been advocated, however, such margins may result in significant morbidity following the resection of even the smallest of tumours. One centimetre 3D-resection margins have been demonstrated as acceptable when dealing with oral and oropharyngeal tumours.[46] By adopting 1 cm surgical margins account is taken for the shrinkage of the specimen that occurs following resection and fixation,[47] so ensuring > 5mm pathological margins. A confounding factor that may need consideration when discussing surgical margins is the resecting modality used, differing modalities resulting in variable shrinkage in animal models.[48] It should be remembered that the use of 5 mm as a cut-off point for 'clear' margins is arbitrary and purely represents a margin that is generally considered acceptable,[49] some believing 3 mm is an acceptable histological margin when considering the need for adjunctive treatment.[50] It is vitally important to continually reassess margins visually and by palpation during tumour resection. Adjuncts to assess margin status include intra-operative tissue staining[51] and ultrasound[52, 53] for deep margins and mucosal staining for mucosal margins.[54] If the resection of a tumour is with curative intent then reconstructive considerations should not influence the tumour resection.

Comparison of published data regarding the incidence of positive margins and their influence on survival or local recurrence is complicated by the variable definition of a positive margin.[55] The definition of a positive margin ranges from invasive tumour at the margin,[56] tumour within 1 mm[46] and tumour within 5 mm.[45] The UK Royal College of Pathologists have issued guidelines suggesting clear margins if the histological clearance is > 5 mm, close margins if 1–5 mm and positive margins if < 1 mm.[57]

The incidence of positive margins for tumours of the oral cavity has been demonstrated as being higher than other head and neck sites,[56, 58] potentially due to its complex anatomy and 3D shape. Large tumours, perineural spread, vascular permeation, a non-cohesive invasive front or cervical metastasis are all associated with a greater risk of failing to achieve clear margins.[44, 59] These features suggest that close or involved margins potentially reflect a more aggressive tumour.[44, 46] The incidence of close or involved margins following tumour resection may be greater than 60% depending on tumour site and size, although 15–20% is more representative.

Invariably it is the deep margin that is close or positive.[60] However close deep margins do not necessarily require adjunctive treatment.[61]

Frozen sections are not routinely used by many surgeons,[44, 46] reasons cited being potential cost,[62, 63] inability to reliably prevent positive final margins,[62, 64] failure to influence 5-year survival or primary failure rates[63] and difficulty in identifying the biopsy site should the result be positive.[65] Ninety-nine percent of American Head and Neck surgeons routinely use frozen section intra-operatively, however over reliance on frozen section may result in under treatment of tumours.[55]

When conducting a bony resection a 1 cm margin should be achieved. It has been demonstrated that it is unusual for extension of tumour in bone to exceed the overlying soft tissue extension, consequently the bony resection should be dictated by the extent of soft tissue disease.

BUCCAL CARCINOMA

Surgical anatomy

The buccal mucosa is the mucosal lining of the inner surface of the cheek. The area extends from the oral commissure anteriorly to the retromolar trigone posteriorly. The junction between the buccal mucosa and retromolar trigone is an arbitrary line drawn from the maxillary tuberosity to the distobuccal aspect of the mandibular third molar (or its anticipated position if not present). The inferior and superior boundaries of the area are delineated by the mandibular and maxillary gingiva-buccal sulci respectively. The WHO classifies this anatomical site as ICD-10 C06.0 and C06.1.[1]

The buccal mucosa is not exposed to masticatory loads and so is covered by a lining mucosa with non-keratinizing stratified squamous epithelium. The mucosa is firmly attached to the underlying buccinator muscle. Minor salivary glands are located within the cheek. The parotid duct pierces the buccinator muscle to enter the oral cavity adjacent to the first maxillary molar tooth.

Sensory innervation to the area is via the buccal branch of the mandibular division of the trigeminal nerve. Lymphatic drainage of the site is via the ipsilateral facial and submandibular nodes to the deep cervical chain. The thickness of the cheek, from mucosal lining to external skin, is 1–3 cm.

Epidemiology

The buccal mucosa is the commonest site for oral cancer in South East Asia, up to 40% of oral cancers arising at this site. This contrasts with North America and Western Europe where buccal carcinoma only accounts for 2–10% of oral carcinomas.[46, 66] The consumption of betel quid is socially and culturally embedded in the countries of South-East Asia and is responsible for the difference in site predilection. The ingredients of Betel quid (Paan/Paan Masala) varies throughout South-East Asia. The main ingredients include the Piper betel leaf, slaked lime, spices, tobacco and areca nut. For many years, the tobacco content alone was credited as being the carcinogenic agent in betel quid, however, it is now recognized that the areca nut is also carcinogenic, as well as being the main aetiological agent in oral submucous fibrosis. Individuals who consume betel quid frequently have a preference regarding which side they chew betel, this corresponding to the side of tumour development. There is a strong association with smoking and alcohol consumption in populations where betel chewing is not prevalent.[66–68]

The male to female ratio in Western countries approximates 1:1, however, in South-East Asia the ratio reflects

the consumption of betel quid. In India, the male to female ratio is approximately 4:1 but in the Taiwanese population, where betel quid users are primarily male, the ratio is as high as 27:1.[69]

Buccal carcinoma typically occurs over the age of 40 years, although it may occur in younger patients,[70] particularly when associated with the habit of betel chewing.[71] Oral submucous fibrosis and lichen planus may involve the buccal mucosa, both being considered premalignant conditions.

Presentation

Buccal carcinoma may be described as verrucous, exophytic or ulceroinfiltrative in character. Patients may present with pain, an intraoral mass, ulceration or trismus. Patients who chew betel often have areas of erythroleukoplakia of the buccal mucosa or submucous fibrosis and consequent trismus, making the detection of invasive squamous cell carcinoma difficult. Advanced buccal carcinomas may extend into adjacent sites to include external skin, mandible or maxilla.

It is not unusual for patients to present with advanced disease, 40% or more presenting with Stage III/IV disease,[66, 67, 72] although earlier presentation has been demonstrated in Western populations.[73] Palpable lymphadenopathy on presentation may be as high as 57% for T3/4 lesions. Occult nodal metastasis may be present in 26% of those who are clinically N0 at presentation.[66, 67, 72, 74] It has been suggested that buccal carcinoma associated with Paan chewing is less likely to metastasize to regional lymph nodes, possibly because of local fibrosis associated with submucous fibrosis.[75] Tumours that are greater than T2, are poorly differentiated, have a poor lymphocytic response[74] or are thicker than 5 mm[74, 76] are more likely to demonstrate cervical metastases. Buccal cancers are usually well differentiated.[66, 77]

Workup

Biopsies of buccal carcinomas should be of sufficient depth to help the pathologist give an indication of depth of invasion, since this will help decide on management of the neck. Buccal carcinoma may rapidly extend to adjacent sites, thus accurate imaging is required. Most patients will require MRI/CT imaging, augmented with ultrasound scan if necessary to help in assessment of depth of primary and cervical lymphadenopathy.

Treatment

PRIMARY SITE

Traditional treatment of buccal carcinoma is surgery with PORT for selected patients.[67, 69] T1/2 disease can typically be resected perorally, however, T3/4 disease may require facial access incisions and bony resection of the maxilla and / or mandible.

The primary tumour should be resected with a 1 cm margin,[46] and up to 2 cm if skin is involved.[78] Facial access incisions (upper or lower lip splits) may be required to facilitate access, particularly in patients with concurrent oral submucous fibrosis. The buccinator muscle should be included as the deep margin at the very least.[78] The parotid duct may need to be repositioned or ligated.[77] Ligation of the parotid duct may result in initial parotid swelling which usually subsides as the gland atrophies. External skin should be taken with the specimen if there is any evidence clinically or on imaging that it is involved. Partial maxillectomy or mandibular resection (rim or segmental) may be required.

Small T1 tumours may be resected and reconstructed by primary closure. Healing by secondary intention may be considered, however, post-operative trismus may be anticipated unless vigorous mouth opening exercises are performed. Split-thickness skin grafts may be used with the aid of silicone sheets to stabilize the graft.[79] The use of a skin graft to reconstruct deeper resections may leave a very thin cheek with potentially poor aesthetics. Local flaps such as the buccal fat pad or temporoparietal fascial flap may be used for reconstruction if tumour extension does not compromise their use. Microvascular free-flap reconstruction with a radial-free forearm flap or anterolateral thigh flap[80] restores the thickness of the cheek and if external skin is involved the flaps can be bi-paddled to provide reconstruction of mucosal and skin surfaces. T4 tumours requiring segmental resection of the mandible may require composite free-flap reconstruction. Reconstruction with a radial-free forearm flap has been shown to give better post-operative mouth opening than reconstruction with a split skin graft or buccal fat pad.[81]

Radiotherapy as a single treatment modality for T1/2 tumours has been advocated,[82, 83] however a change of practice from radiotherapy to surgery at Memorial Sloan Kettering was associated with improved prognosis.[84] Brachytherapy or external beam irradiation may be considered.

NECK

Regional spread of disease in buccal carcinoma is usually to the ipsilateral level I and II lymph nodes.[85, 86] Unlike carcinoma of the oral tongue, skip metastases to level IV of the neck are unusual.[75] It has been suggested patients with palpable lymphadenopathy or pathological nodes on imaging should have a comprehensive neck dissection, although if pathological nodes are only located in level Ia level I–III SND may be considered.[87] Nodes in the region of the facial artery as it crosses the mandible should be removed with the neck dissection specimen.

Patients with T2 or greater primary tumours or tumours with a thickness > 5mm should have an END.[67, 88] Some institutions will conduct an END if the tumour is 3–4 mm thick or if histological examination the tumour demonstrates lymphatic infiltration.[67]

PORT

The indications for PORT to the locoregional area are similar to other sites, notably 2 or more nodes in the neck,

extracapsular spread, positive margins or margins less than 3 mm[89] and stage III/IV disease.[72] The beneficial role of PORT in selected patients with buccal carcinoma has been demonstrated by several authors.[90, 91] Some authors suggest that PORT should be considered even in stage I and II disease,[66, 72, 92] or tumours greater than 10 mm thick.[90]

Recurrence

Recurrence rates for buccal carcinoma are 26–80%,[66, 67, 69, 72, 74, 77] usually occurring within 2 years.[67, 69, 77] Involvement of the parotid duct and buccinator have not been found to be significant indicators of recurrence.[66] Factors that influence recurrence include tumour thickness,[74, 76, 93] histological margins less than 3 mm[89] and tumour differentiation.[77] It has been demonstrated that following treatment for buccal carcinoma, distant failure is more common than regional failure compared to tongue carcinoma,[94] although survival rates are similar for both.[94, 95]

Prognosis

Buccal carcinoma is considered by many to be particularly aggressive,[73, 96] but not universally so.[95] Five-year survival figures vary depending on population studied and treatment modality.[67, 72, 97]

Factors that potentially influence survival include regional metastasis,[67, 98] extracapsular spread,[67, 97] tumour thickness >5–6 mm,[74, 76] skin involvement,[69] histological margins less than 2 mm[89, 97, 99] stage[71] and recurrent disease.[74]

KEY POINTS

- Commonest site for oral cancer in South East Asia.
- Associated with Betel / Paan consumption.
- Good surgical reconstruction is required to prevent post-operative trismus.
- Up to 26% have occult nodal metastasis at presentation.
- Consider END (Levels I–III) if tumour >4 mm thick.

FLOOR OF MOUTH CARCINOMA

Surgical anatomy

The floor of mouth is the mucosal lining of the anterior and lateral floor of the mouth. The area is bound anteriorly and laterally by the attached mucoperiosteum of the mandibular alveolus. The lateral floor of mouth is bound posteriorly by the anterior tonsillar pillars. Medially the floor of mouth merges with the ventral and lateral aspects of the tongue. The WHO classifies this anatomical site as ICD-10 C04.[1]

The floor of mouth is lined by non-keratinizing stratified squamous epithelium similar to the buccal mucosa, but with a less dense submucosa. Underlying the mucosa lie minor salivary glands, the sublingual glands, submandibular ducts, hypoglossal nerves, lingual nerves and genioglossus muscles. These structures are located in an area bound by the mylohyoid muscle laterally and hypoglossal muscle medially. The submandibular ducts enter the mouth anteriorly either side of the lingual frenum.

Sensory innervation to the area is by the lingual branch of the mandibular division of the trigeminal nerve. Lymphatic drainage of the lateral floor of the mouth is via the ipsilateral submandibular nodes to the deep cervical chain. Lymphatic drainage of the anterior floor of mouth is via the submental nodes to both the left and right deep cervical chains.[100] Lingual lymph nodes in the floor of mouth, located above the mylohyoid, may have implications in the management of tumours of the floor of mouth.[86, 101]

Epidemiology

The floor of mouth is a common site for oral cancer, 18–33% of oral cancers developing at this site.[46, 102–105] It is thought that the high incidence of cancer at this site may be due to pooling of saliva with dissolved carcinogens or lack of keratinized epithelium.[106] Within this anatomical site tumours are more likely to occur anteriorly.[107–109]

Floor of mouth carcinoma occurs more frequently in men,[104, 105, 108, 110, 111] the age at diagnosis usually being in the 6th–7th decade.[104, 110, 111] Floor of mouth cancer, as does oral cancer at all sites, has a strong association with smoking[106] and the consumption of alcohol.[110]

Presentation

Since the floor of mouth is a relatively small anatomical area, tumours frequently extend into adjacent sites notably the tongue or mandible.[112] Patients may present with a sore lesion, ulceration or obstructive submandibular gland symptoms.[113] Leukoplakia of the floor of mouth may be considered a premalignant condition with an annual transformation rate of 1–2.9%,[114, 115] and it is not uncommon to find a carcinoma focus within an excised leukoplakic lesion.

Stage at presentation varies considerably between institutions, although approximately 50% present with advanced disease.

Cervical lymphadenopathy is present in 17–45% of patients on presentation,[104, 105, 108, 116] up to 22% of those clinically N0 at presentation having occult metastasis.[104, 111, 116, 117] Depending on the location of the tumour up to 28.6% of patients may have bilateral nodal involvement.[105, 116] Many tumours of the floor of mouth are well or moderately differentiated.[108]

Workup

Workup of patients with floor-of-mouth tumours should follow that of any patient with oral cancer. Particularly important in larger floor of mouth tumours is assessment of invasion of the base of tongue or mandible. The loose connective tissue of the floor of mouth presents a poor barrier to local spread.

Treatment

PRIMARY SITE

The need for aggressive treatment of floor-of-mouth carcinomas is well recognized.[118]

Surgical resection with a 1 cm margin should be achieved if surgery is the preferred treatment modality. Even in the best surgeons' hands positive or close margins may be seen in up to 47% of resections,[104, 112] despite the use of intraoperative frozen section.[105] Many floor-of-mouth tumours are infiltrative with indistinct edges, possibly explaining the high incidence of positive margins.[105] Further resection is advocated if margins are positive.[105] Although 1 cm margins are considered by most surgeons to be adequate, extended 2 cm margins have been advocated by some.[119]

The early extension of floor-of-mouth tumours into the tongue or mandible is demonstrated by the fact that many patients require rim or segmental resection of the mandible.[104] Surgical resection of the floor of mouth in the majority of circumstances will involve resection of part of the submandibular ducts. Typically the ducts will be transected at the resection margin, well away from their orifice, although in smaller resections at least 3 mm length of duct proximal to the orifice should be taken to ensure surgical clearance of carcinoma or dysplasia that may extend along the duct.[120] Management of the submandibular ducts is of great importance if a neck dissection is not being conducted with consequent removal of the submandibular gland. Stricture of the duct in the presence of a functioning gland may give rise to obstructive symptoms of the gland and difficulty in differentiating the potential submandibular gland swelling from cervical disease. The ducts should be transected obliquely to minimize stricture formation and repositioned at the margin of resection, ideally being stented.[121] Alternatively, the ducts may be found proximal to the resection margin, a longitudinal incision made and the duct 'marsupialized' to the floor-of-mouth mucosa. Uninvolved branches of the lingual nerve should be identified and preserved.

Small resections may be left to heal by secondary intention or a split-thickness skin graft applied. It has been demonstrated that a better functional outcome is achieved with primary closure, however, this naturally can only be achieved with the smallest of tumours.[122]A more substantial reconstruction may be achieved using local nasolabial[123] or facial artery musculomucosal flaps,[124] but an edentulous segment is required when using both of these flaps to accommodate their pedicle. If a neck dissection is required and surgical facilities allow, microvascular reconstruction provides a far more flexible reconstructive option, without necessarily prolonging operative time if a two-team approach is adopted. The radial free-forearm flap is an ideal reconstructive option for floor-of-mouth defects, easily being converted to a composite flap if segmental resection of an edentulous mandible is required. Prefabricated fasciomucosal free flaps have been described in oral reconstruction,[125] however their role in oncological reconstruction is questioned. The fibula osteocutaneous flap provides superior reconstruction if a segmental resection is anticipated in a dentate patient, but unlike the composite radial free flap, flexibility of the skin paddle is limited. The scapula osteocutaneous flap with two skin paddles, or one skin paddle and muscle left to mucosalize, provides an excellent reconstruction of large defects involving mucosa, bone and external skin.

Radiotherapy techniques (brachytherapy or external beam) for T1/2 primaries have been shown to provide results similar to surgery.[108, 109, 126] The proximity of the floor of the mouth to the mandible is of concern when using brachytherapy since up to 8.5% of patients treated with this modality require segmental resection of the mandible due to osteoradionecrosis within 10 years.[108, 109]

Several units have described a change in practice from brachytherapy to surgery as the primary treatment modality due to the risk of complications.[105, 111, 127] T3/4 lesions are best treated with surgery and PORT.

NECK

Regional spread of disease in floor-of-mouth carcinomas is usually due to the ipsilateral level I to III lymph nodes,[86, 111] with involvement of multiple levels not being unusual. Lesions towards the midline may spread to both sides of the neck, hence bilateral neck dissections should be considered. The presence of lingual lymph nodes has raised the concept of in-continuity neck dissection[128] in an attempt to reduce local recurrence and improve survival. Resection of the tumour accompanied with the complete clearance of the floor of the mouth, preserving mylohyoid, hyoglossus and genioglossus if possible, so clearing the lingual lymph nodes would seem an acceptable method of managing lingual lymph nodes.[101]

The decision to perform an END has been related to tumour size or depth of invasion. Lesions that are T2 or greater should have a I–III/IV selective neck dissection,[104, 129] although ENDs have been advocated for T1 lesions.[108, 129]

Tumour thickness of 4 mm is often used as a 'generic' critical thickness, greater than which an END is indicated, since the risk of occult metastasis is greater than 20%.[130] It has been demonstrated that the risk of cervical metastasis of floor-of-mouth tumours exceeds 20% in tumours as thin as 1.5–2 mm.[131, 132] Using a thickness of 1.5 mm may result in up to 32% of patients requiring END based on thickness criteria.[131]

PORT

The indications for PORT to the locoregional area are similar to other sites, notably two or more involved nodes in the neck, extracapsular spread, positive margins or stage III/IV disease.

The beneficial role of PORT in selected patients with floor-of-mouth carcinoma has been demonstrated.[104, 112, 116]

Recurrence

Recurrence rates for floor-of-mouth carcinoma are 26–55%,[104, 111, 118] usually within the first 2 years.

Factors that influence recurrence include tumour size,[104, 111] margin status[104, 105] and tumour thickness[132] and advanced nodal disease.[111]

Prognosis

Overall 5-year survival for floor-of-mouth carcinoma is 52–76%.[104, 105, 111, 116] Factors that potentially influence survival include nodal status,[105, 116] thickness,[23] margin status and recurrence.[105]

KEY POINTS

- One of the commonest sites for oral cancer.
- Leukoplakia of the floor of mouth has a 1–2.9% annual malignant transformation rate.
- Careful consideration should be given to management of the submandibular ducts.
- Anterior lesions may require treatment of both necks.
- Tendency for cervical metastasis to occur in thinner tumours than other sites.

TONGUE CARCINOMA

Surgical anatomy

The oral tongue is the freely mobile anterior two-thirds of the tongue, demarcated from the base of tongue by the circumvallate papillae posteriorly. The tongue may be subdivided into the tip, dorsum, lateral borders and ventral surface. The WHO classifies this anatomical site as ICD-10 C02.[1] The ventral and lateral surfaces are in continuity with the floor of mouth, having a lining mucosa with non-keratinizing stratified squamous epithelium. The dorsum and tip of tongue are lined by specialized gustatory mucosa, with a thick, primarily keratinized epithelium. The mucosa of the tongue overlies the intrinsic muscles of the tongue, in addition to the four paired extrinsic muscles of the tongue: genioglossus, hyoglossus, styloglossus and palatoglossus.

Motor innervation to muscles of the tongue is via the hypoglossal nerve, except palatoglossus which is supplied by the vagus nerve. Sensation of the tongue is supplied by the lingual nerve, a branch of the mandibular division of the trigeminal nerve. Taste sensation of the oral tongue is supplied by fibres of the facial nerve that run with the lingual nerve before passing to the chorda tympanic branch of the facial nerve.

Lymphatic drainage of the lateral borders of the tongue is to the ipsilateral cervical nodes; however drainage of the midline, tip and base of tongue occurs bilaterally. The blood supply to tongue is provided by the paired lingual arteries, the third branch of the external carotid artery. During resection of posterior tongue lesions the contralateral vascular pedicle should be preserved if the tongue tip is to be maintained. The tongue is a complex structure with an important role in mastication, deglutition and speech.

Epidemiology

In populations where tobacco chewing is not endemic the oral tongue is one of the commonest sites for oral cancer, with 22% to 39% of oral cancers developing at this site.[46, 103, 133]

Within the site most tumours occur in the middle third of the tongue,[134, 135] commonly on the lateral aspect, followed by the ventral aspect of the tongue. Only 4–5% of tongue carcinomas occur on the dorsum of the tongue.[136]

Tongue cancer occurs slightly more frequently in males,[134, 137–140] the age at diagnosis usually being in the 6th–8th decade[134, 138, 139] and 90% of patients are over 40 years of age.[137] The male to female ratio has decreased in recent years, possibly due to increased alcohol consumption by females. Up to 70% report significant tobacco and alcohol use.[134]

Presentation

Patients with tongue cancer may present with several symptoms notably pain, ulceration or a lump on the tongue.[134, 137, 139, 141] Lesions of the oral tongue are more likely to be symptomatic than lesions of the base of tongue but despite this many patients still present with a 4–6 month history of symptoms prior to seeking medical advice.[137, 139, 142] The majority of patients with cancer of the oral tongue present with stage I/II disease,[134, 137, 138, 141] which contrasts significantly with cancers of the base of the tongue that are usually stage III/IV at presentation.[137] Clinically positive cervical lymphadenopathy at presentation is in the region of 21–34%.[134, 138, 140] Occult cervical metastasis has been demonstrated in up to 53% of patients with tongue cancer[134, 139, 142, 143] and may be related to tumour thickness.[144] Tumours arising on the lateral aspect of the tongue tend to be thicker than those of the ventral aspect of the tongue.[140] Up to 4.5% may have occult cervical disease in the contralateral neck.[139] Clinical examination, CT and MRI have relatively poor sensitivity at determining cervical lymphadenopathy.[140, 145]

The majority of tongue tumours are well to moderately differentiated on histological examination.[134, 137, 138, 141]

Workup

As with many sites management of the neck is frequently determined by tumour thickness. Tumour thickness can be assessed accurately with intraoral sonography, or immediate sonography of the resected tumour[52, 146] prior to proceeding to a neck dissection if access to the neck is not required for reconstructive purposes.

Biopsies should endeavour to include the deep margin of the tumour in addition to mucosa at the periphery of the tumour. Deep biopsies may give an indication of tumour depth, but also multifactorial histological malignancy grading of the most dysplastic areas of the invasive front may help in assessing the risk of cervical metastasis.[140]

Treatment

PRIMARY SITE

Resection of the tumour with a 1 cm margin in three dimensions should be conducted if surgery is the treatment of choice. The use of ultrasonography to aid in assessment of surgical clearance has been advocated,[52, 147] particularly for the deep margin. Frozen section is not routinely used in many units. Even with apparently adequate margins during surgery, 10% of resections may demonstrate histologically positive margins.[134]

Resection of tongue tumours using a 'compartmental' approach as adopted by musculoskeletal oncology surgeons has been advocated,[148, 149] with improved outcomes with this technique.[150]

The aim of reconstruction of the oral tongue following resection is to ensure maximum function of the residual tongue tissue, since the complex function of the tongue cannot be replicated with current reconstructive techniques.[151] Preservation of the tip of the tongue, while maintaining oncologically sound resection margins, helps maximize post-operative function.[152]

The use of monopolar electrocautery, 'cutting' through mucosa changing to 'coagulation' when in muscle, or the harmonic scalpel helps reduce bleeding during the resection, however this is at the cost of lack of feel afforded by the use of scalpel or scissors. If both lingual vessels are resected then the viability of the tip of tongue remnant should be carefully assessed. Sacrifice of both hypoglossal nerves results in a non-functioning tongue tip with consequent poor function.

Functional outcomes following reconstruction of the oral tongue are increasingly being scrutinized since many reconstructive methods are increasingly resource intensive.[153, 154] Small lesions may be removed with a laser and allowed to heal by secondary intention. T1 and small T2 primary tumours may be excised with a vertical wedge and the defect closed primarily, if the defect does not extend to significantly include the floor of mouth. Many larger lesions benefit from free-flap reconstruction of the defect, usually with a radial free-forearm flap, although the anterolateral thigh free flap is being used more frequently. The skin paddle of the chosen free flap should be fashioned so as not to restrict residual tongue function and should hopefully augment swallowing. Typically, the reconstruction should be of the same size, or slightly smaller than the defect created by the resection. Care should be taken in the design of the flap when the defect extends to include adjacent sites such as the soft palate or floor of mouth. The mobile tongue and floor of mouth should be 'separated' in the reconstruction to minimize restriction of movement of the residual tongue.[151] Thin radial free flaps may have their bulk increased by extending fascial flaps beyond the skin island, the fascial flaps then being folded and buried underneath the epithelial reconstruction.[151]

Reconstruction of large resections may be accompanied by measures aimed to improve post-operative function such as static laryngeal suspension to the mandible and cricopharyngeal myotomy.[151] Once the specimen is removed it is examined for clearance and orientated for the pathologist, supplemented by a digital photograph.

Radiotherapy as the primary treatment modality has been advocated since it conserves tongue volume and morphology, brachytherapy being considered preferable to external beam radiotherapy.[153] Osteoradionecrosis of the mandible is a recognized complication of brachytherapy of the tongue, up to 9% developing some form of osseous complication.[138] The use of brachytherapy to the primary site requires either surgery or external beam radiotherapy to the neck in an elective or therapeutic manner. When surgery is not used as the primary treatment valuable histological prognostic information is lost. This makes the decision as to whether to conduct an END more difficult. It has been suggested that surgery is superior to brachytherapy in the management of Stage I/II tongue cancer.[154] Surgery as the primary treatment modality ensures that radiotherapy is kept in reserve for either poor prognostic indicators of the resected specimen, for management of recurrence or management of second primaries which may occur at a later date.

NECK

Tumours of the tongue initially metastasize to levels I and II, lateral tongue tumours frequently metastasizing directly to level II nodes.[86] Involvement of level V nodes, in the absence of positive nodes in levels I–IV is rare, however, it is not unusual for nodes in level IV alone to be involved.[140, 155] Hence, in ENDs levels I–IV should be dissected, taking care to manage the thoracic duct appropriately which is the main cause of surgical complication in this area.

Like floor-of-mouth tumours the presence of lingual lymph nodes should be considered and either an in-continuity resection with the neck specimen or clearance of tissue above mylohyoid conducted.[156]

Bilateral neck dissections should be considered in tumours that extend to or beyond the midline, the use of frozen section on ipsilateral nodes having been proposed as method of identifying those in which a contralateral node may be indicated.[157]

The management of the neck in larger primary tumours is usually straightforward since the neck is accessed for microvascular or pedicled flap reconstruction of the primary site. Management difficulties arise with smaller tumours amenable to per oral resection and local closure.[144]

It has been proposed that the increased incidence of nodal metastasis associated with tongue carcinoma may be due to contraction of tongue muscle promoting entry of cancer cells into the lymphatics.[158] It is thought that the mechanism by which tumour thickness is related to cervical metastasis is that thicker tumours have access to wider lymphatics in which tumour emboli can form more readily.

Although tumours arising on the lateral aspect of the tongue tend to be thicker than those of the ventral aspect of the tongue,[140] this may not manifest as a greater risk

of cervical metastasis, since the 'critical thickness' for tumours of the floor of mouth is less than other oral sites.

END or elective neck radiotherapy should be considered for tumours thicker than 3–4 mm,[144, 159, 160] T2 or greater in dimension and T1 tumours that demonstrate poor histological features (poor differentiation, double DNA aneuploidy or degree of differentiation at the advancing front).[135, 160]

A recent randomized trial has largely settled the controversy about elective vs therapeutic neck dissection in the setting of the N0 neck. D'Cruz et al. reported on the oncologic outcomes of 500 patients (245 in the elective-surgery group and 255 in the therapeutic-surgery group), with a median follow-up of 39 months. At 3 years, elective node dissection resulted in an improved rate of overall survival (80.0%; 95% confidence interval [CI], 74.1–85.8), as compared with therapeutic dissection (67.5%; 95% CI, 61.0–73.9). END was associated with a reduced hazard for death in the elective-surgery group (0.64; 95% CI, 0.45–0.92; P=0.01). Patients in the elective-surgery group also had a higher rate of disease-free survival than those in the therapeutic-surgery group (69.5% vs. 45.9%, P<0.001).[159]

Other studies with similar have also demonstrated the survival advantages of END.[142, 143]

PORT

PORT has been advocated for positive margins,[134, 135] multiple cervical nodes,[135] extracapsular spread in the neck,[135] Stage III/IV disease,[134, 135] perineural spread[135] or tumours thicker than 9–10 mm even in the absence of other features.[144, 158, 161] Based on involved margins, ECS of cervical nodes or multiple positive nodes 26–62% of patients receiving surgery as the primary treatment modality may require PORT.[140, 162]

Local failure following PORT to tongue tumours has been demonstrated to be higher than comparable floor-of-mouth tumours, leading some to suggest higher doses of PORT should be considered for tongue tumours.[112]

Recurrence

Recurrence rates for oral tongue carcinoma are 10–50%,[139, 144] usually being locoregional.[134, 140]

Similar to other sites, recurrence usually occurs within the first 2 years.[134, 141]

Factors that influence local recurrence include tumour thickness and the presence of perineural spread.[144, 162] It has been proposed that recurrence of thicker tumours is related to difficulty in assessing deep clearance intraoperatively compared to assessing mucosal clearance.[158]

Patients younger than 40 years have been demonstrated to be significantly more likely to develop locoregional failure, although this does not influence survival.[163] Metachronous second tumours are seen in nearly 10% of patients who have had tongue cancer.[139]

Prognosis

Clinical features of tongue carcinoma remain the most reliable prognostic indicators, although histological characteristics contribute to prognostication.[164] Tumour thickness,[132, 140, 159, 160, 162] the presence of perineural invasion,[144, 162] cervical metastasis[139, 134] or dysplasia at the resection margins[160] have all been demonstrated to influence prognosis. Patients with tumours greater than 9 mm thick have been shown to have a 5-year survival of 66% compared to 100% survival for tumours less than 3 mm thick.[144] It has been reported by several groups that younger patients without usual risk factors have a poorer long-term prognosis.[164, 165]

KEY POINTS

- One of the most common sites for oral cancer.
- Usually presents as Stage I/II disease.
- ENDs should include levels I–IV because of skip metastases.
- Reconstruction should maximize function of the residual tongue.

RETROMOLAR CARCINOMA

Surgical anatomy

The retromolar trigone is a triangular area of mucosa that overlies the ascending ramus of the mandible. The base of the triangle is in the region of the mandibular third molar inferiorly, the apex being adjacent to the maxillary tuberosity superiorly. The area is bound by the buccal mucosa laterally and the anterior tonsillar pillar medially. The WHO classifies this anatomical site as ICD-10 C06.2.[1] The retromolar mucosa is not exposed to masticatory loads and so is covered by a lining mucosa with non-keratinizing stratified squamous epithelium, similar to the buccal mucosa. Sensory innervation to the area is by the buccal branch of the mandibular division of the trigeminal nerve. Lymphatic drainage is to the ipsilateral submandibular and deep cervical nodes.

Epidemiology

The retromolar trigone is a relatively unusual site for carcinoma of the oral cavity, only 6–7% of oral carcinomas arising at this site.[46, 164] The disease is more common in males and like other sites is typically a disease of older individuals.[164–166] Common with other oral sites, there is a strong association with smoking[166, 167] and alcohol consumption.

Presentation

Patients typically present late with pain, trismus, otalgia or lingual parathesia.[164, 167, 168] Since the retromolar tigone is an anatomically small-site tumour which often extends to involve adjacent subsites – buccal mucosa in 84%, oropharynx in 14%, masticator space (medial pterygoid, masseter, temporalis, mandibular branch of the trigeminal nerve) in 22%. Bone involvement of the mandible or maxilla is present in 12–34%[164, 166–169] of retromolar tumours, although a higher incidence of up to 75%

has been reported.[170] The posterior maxilla is more frequently involved than the mandible when bone invasion occurs.[166] Tumour extension into the masticator space or lower pterygoid plates classifies tumours in this area as T4b, however, if resectable outcomes are comparable to T4a tumours.[171]

Retromolar carcinoma usually presents as advanced disease, 55–73% having Stage III/IV disease at presentation.[164–166] Spread to regional lymphnodes occurs in 26–56% of patients at presentation,[164, 166, 172] 8–15% having occult cervical node involvement.[164, 172]

Tumours of the retromolar trigone are usually well or moderately differentiated.[166]

Workup

The complex anatomy of the retromolar region and the frequent extension of retromolar carcinoma make accurate preoperative imaging essential. Clinical examination alone is not reliable at determining underlying bone involvement.[173] CT has been demonstrated to have a high specificity, but low sensitivity for predicting mandibular bone invasion of retromolar carcinomas.[170, 174] MRI is considered the imaging modality of choice for retromolar tumours due to its ability to accurately stage the disease and demonstrate accurately anatomical relationships of the tumour,[175] although mandibular invasion may still be hard to define.

Treatment

PRIMARY

The treatment of choice for retromolar tumours is surgical resection with pre/post-operative radiotherapy or chemoradiotherapy dependant on stage of tumour and histological findings.[164–166, 168, 169, 173] Radiotherapy as a sole treatment modality for retromolar carcinoma has been demonstrated to be associated with significantly worse recurrence rates and disease-free survival,[165, 166] although others have been unable to demonstrate this significance.[167, 176] The debate regarding the use of surgery or radiotherapy as the primary treatment modality is hampered by the lack of data regarding tumour thickness in this anatomical site. It is recognized that tumours in this site may be T3 in size, but superficial in nature.[177]

Resection should be achieved with a 1 cm margin in all planes. It is recognized that the incidence of positive margins following resection of retromolar tumours is higher than other oral sites.[44]

Small tumours of the retromolar trigone may be resected via a transoral route, however, the posterior location of retromolar tumours and frequent extension of disease into adjacent anatomical sites often necessitates a mandibulotomy to facilitate access.[164, 168] Extensive tumours extending into the masticator space may require a cervicofacial incision, parotidectomy, +/– zygomatic osteotomy and preservation of the facial nerve for access, or an anterior approach including maxillectomy.[178]

Defects following the resection of small mucosal tumours may be left to heal by secondary intention, however, larger lesions require reconstruction to prevent trismus. Simple reconstructive methods include use of a split-skin graft or buccal-fat pad reconstruction. Tongue flaps and masseteric flaps have been described,[169] however they lack flexibility and may be compromised in anything but the smallest of tumours.

Given the low-negative predictive value of CT for bone involvement and the high incidence of bone involvement demonstrated in retrospective series, a low threshold for bone resection should be adopted.[173] A posterior marginal mandibulectomy (including coronoid) conducted via a visor or lip split soft-tissue flap is oncologically safe in patients with no history of previous radiotherapy and no radiological signs of cortical bone involvement.[168, 179] Patients demonstrating cortical bone involvement on imaging, or who have previously received radiotherapy, should have a segmental mandibular resection. A posterior maxillectomy should be conducted when indicated.

The combination of mandibulotomy and posterior marginal mandibulectomy for large soft tissue lesions should be avoided in view of the increased risk of osteoradionecrosis; a segmental resection is warranted in these circumstances.[180]

Pedicled myocutaneous flaps such as the pectoralis major flap are stretched to their limit at this anatomical site, often resulting in delayed healing.[168] The use of the radial free-forearm flap or anterolateral thigh flap provides excellent reconstruction of larger soft-tissue defects in the retromolar region. Where the resection involves the soft palate, the combination of free flap and superiorly based pharyngeal wall flap should be considered to minimize nasopharyngeal reflux.

Reconstruction following segmental resection should ideally be with free-tissue transfer such as the fibula, scapula or DCIA flaps. Since radiotherapy will almost certainly be indicated following segmental resection the use of vascularized bone flaps results in more predictable healing with lower risk of non-union or resorption.[168] The use of reconstruction plates and soft-tissue cover alone is particularly prone to failure in the retromolar region.[181]

Large tumours extending into mandible, maxilla, soft palate, tongue base and buccal mucosa require careful consideration regarding reconstructive options. Dual free flaps may provide ideal soft tissue and bony reconstruction but at the increased risk of complications. The scapula flap is versatile enough in thin individuals to be able to reconstruct these extensive defects.

NECK

Lymphatic spread to the neck is usually to levels I and II in the absence of detectable lymphadenopathy, however, involved nodes in levels III–V may occur in the presence of nodes in levels I and / or II.[172]

Unlike tumours at other sites there are little data correlating tumour thickness to incidence of cervical metastasis.

An END (levels I–III/IV) is indicated for any tumour bigger than T1,[164, 168, 172, 179] or where access to vessels in the neck is required for reconstruction.

PORT

Up to 58% of patients may require PORT/chemoradiotherapy,[164] an indication of the typically advanced nature of retromolar carcinomas.

Recurrence

Local and/or regional recurrence may occur in 20–37%,[164–166] depending on primary treatment modality and stage of disease on presentation. Recurrence usually occurs in the first 2 years.[172]

Prognosis

Factors influencing survival are stage, involvement of the masticator space[164] and cervical metastasis,[166, 168, 174] mean survival in patients with masticator space involvement being 38 months.[164] Patients receiving surgery combined with radiotherapy have been demonstrated to have a significant survival advantage over patients receiving radiotherapy alone.[165]

KEY POINTS

- 6–7% of oral carcinomas.
- Frequently presents as Stage III/IV disease with extension into adjacent sites.
- Accurate preoperative imaging is required to determine extent of disease.

MAXILLARY ALVEOLUS AND HARD PALATE

Surgical anatomy

The maxilla comprises the maxillary alveolus and the hard palate. The osseous alveolar process supports the maxillary dentition, being covered by a mucoperiosteum with a stratified squamous epithelium. The maxillary alveolus merges laterally with the buccal mucosa and lips at the gingival sulcus and medially with the hard palate. The alveolar process extends to the upper end of the pterygopalatine arches posteriorly. The hard palate lies within the horseshoe shape of the maxillary alveolus, merging imperceptively with the alveolar mucosa. The hard palate has minor salivary glands located in the submucosa, 33% of palatal tumours being derived from salivary epithelium.[182] Posteriorly, the hard palate merges with the soft palate at the posterior edge of the palatine bone. The WHO classifies these anatomical sites as ICD-10 C05.0 (hard palate) and C03.0 (maxillary alveolus).[1] Sensory innervation to the maxillary mucosa is by branches of the maxillary division of the trigeminal nerve. The nasopalatine nerve supplies the anterior hard palate, passing through the incisive foramen, the posterior palate being supplied by the paired greater palatine nerves that pass through the greater palatine foraminae. Lymphatic drainage is to the ipsilateral cervical nodes via the submandibular nodes or potentially the retropharyngeal nodes in posteriorly located tumours.

Epidemiology

Squamous cell carcinoma of the maxillary alveolus represents 3.5–6.5%[60, 103] of oral cancers, being approximately one-third as common as mandibular alveolar carcinoma. Carcinoma of the hard palate is very unusual representing only 1–3%[183, 184] of oral cancers. Aetiological factors include tobacco use and alcohol consumption. Palatal carcinoma is particularly associated with reverse smoking, a habit practised in parts of India by women.[185–187]

Patients tend to present in their 6th–7th decade of life.[183, 186, 188] There is an even distribution between the sexes, except where reverse smoking is practised when there is a greater frequency in females.[186]

Presentation

Patients may present with pain, ulceration, loose teeth or poorly fitting dentures. Symptoms of advanced disease may include infraorbital parathesia, trismus or nasal obstruction. Most patients present with Stage I or II disease.[183, 188]

Approximately 8% of patients with carcinoma of the hard palate or maxillary alveolus present with cervical lymphadenopathy, a further 27% having occult metastasis.[188]

Workup

The surface extent of a maxillary carcinoma may be relatively easy to determine from clinical examination alone, however, extension into the maxillary antrum and beyond requires additional imaging. Extension of tumour through the pterygoid plates into the masticator space may render a tumour inoperable. CT scans and MRI are complementary in the assessment of maxillary tumours.[189]

Intranasal examination with a nasendoscope should be conducted to determine the extent of tumour through the floor of nose or medial antral wall.

All patients should have impressions taken for the provision of a temporary obturator, even if free-flap reconstruction is anticipated. In the unfortunate situation of free-flap failure the presence of pre-surgical models will make prosthetic salvage considerably easier. If prosthetic reconstruction is to be considered from the outset then early consultation with a prosthodontist is required.

Treatment

PRIMARY

Anaesthesia is usually accomplished with an oral tube, a tracheostomy only being considered for larger resections or free-flap reconstruction. Patients requiring an upper cheek flap for access should have their eyes protected with corneal shields or temporary tarsorraphies.

The surgical goals that apply to hard palate and maxillary alveolar tumours are the same as those at other sites, notably surgical clearance of 1 cm in three dimensions. Small tumours may be approached per orally, however larger tumours may require an upper cheek flap or midfacial degloving to augment access.

Once the mucosal incisions have been completed the soft tissues are elevated in a subperiosteal plane away from the tumour to allow access for bone cuts. Teeth may need to be extracted to allow osteotomy cuts and minimize post-operative complications. The use of a fine reciprocating or saggital saw allows accurate bony resection. Care should be taken to avoid tooth roots. If the margins of resection extend posteriorly the specimen may be disarticulated from the pterygoid plates with a curved osteotome. Posterior dissection may be completed with large curved scissors. The posterior dissection in the region of the pterygoids should be last part of the resection due to the bleeding that occurs in this area. An ipsilateral coronoidectomy should be conducted to minimize impingement of the coronoid on the prosthesis or flap reconstruction. Defects that are to be reconstructed with a prosthesis should be lined with a split skin graft.

Surgical closure of small maxillectomy defects may be achieved with local flaps such as buccal fat pad, temporalis flaps or facial artery musculomucosal flaps. Large defects may require soft tissue[190] or composite free tissue transfer.[191] The use of an appropriate defect classification system[194] allows for planning of reconstruction and communication with colleagues.

NECK

Historically, regional spread from maxillary tumours has been considered low, however this may be due to coregistration of hard palate and alveolar tumours as sinonasal tumours.[182] Cervical metastasis has been demonstrated in 35% of patients with hard palate or maxillary alveolar carcinomas,[188] an elective I–III neck dissection being considered appropriate for lesions of T2 size or greater.[182, 192] Consideration should be given to clearing the facial lymph nodes when conducting a neck dissection for maxillary tumours.

PORT

PORT has been suggested for T3 or greater disease, positive margins, perineural or perivascular invasion or multiple cervical nodes, particularly if they demonstrate extracapsular spread.[182]

Recurrence

Locoregional control of hard palate and alveolar tumours following initial therapy is in the region of 40–45%,[183, 188] increasing to 68% following secondary intervention.[183] Salvage of local recurrence may be achieved in 33% and regional recurrence in 71%.[188] Over 90% of recurrences occur within the first 2 years, similar to other sites.

Prognosis

The 5-year absolute survival for hard palate carcinoma is 57%, 5-year survival for alveolar carcinoma being 49%.[185] Tumour stage and presence of cervical metastasis influence long-term survival.[183] The origin of maxillary carcinoma (oral vs sinus) does not influence long-term prognosis.[193]

Current staging of maxillary tumours categorizes a tumour as T4 if cortical bone is breached. It has been suggested that a more accurate prognostic indication is given if T4 is reserved for tumours that breach the nasal or sinus floor.[194]

KEY POINTS

- Carcinoma of the maxillary alveolus is three times less common than the mandibular alveolus.
- Carcinoma of the hard palate represents only 1–3% of oral cancers.
- Palatal carcinoma is associated with reverse smoking.
- All patients should have dental impressions as part of their workup.
- Some degree of bone removal is nearly always required.
- Selective neck dissection is often indicated.

MANDIBULAR ALVEOLUS

Surgical anatomy

The mandibular alveolus represents that part of the mandible that is 'intraoral'. The osseous alveolar process of the mandible supports the dentition and is covered by a mucoperiosteum. The mandibular alveolus merges laterally with the buccal mucosa/lips at the gingival sulcus and medially with the floor of mouth. The alveolar process extends to the retromolar trigones posteriorly. The WHO classifies this anatomical site as ICD-10 C03.1.[1] Sensory innervation to the mandibular alveolus is by the mandibular division of the trigeminal nerve. Lymphatic drainage is to the ipsilateral submandibular and submental nodes to the deep cervical chain. Lymphatic drainage towards the midline may be bilateral. Following loss of the dentition there is considerable resorption of the alveolar process, leaving only a thin strip of attached mucoperiosteum on the crest of the mandible between the floor-of-mouth and buccal mucosa.

Epidemiology

Squamous cell carcinoma of the mandibular alveolus represents 7.5–17.5%[60, 103, 184] of oral cancers, although it represents up to 30% of oral cancers in the Japanese population.[195] Mandibular alveolar carcinoma is three times more common than maxillary alveolar carcinoma.[196] Rarely primary intraosseous carcinomas may occur, being derived from residues of odontogenic epithelium within the mandible.[197] The use of tobacco, particularly chewing tobacco, and alcohol is associated with alveolar carcinoma.

Patients tend to present later in life in their 7th decade, the disease being slightly more common in males.[195, 196, 198]

Presentation

The most common presenting symptom is pain, occurring in 54–86% of patients.[195, 196, 198] Patients who are dentate may note loosening of teeth while edentulous patients may note a change of fit of their dentures. Labial parathesia may be a presenting feature in up to 14% of patients. Unfortunately patients still present with a history of delayed healing of an extraction socket in up to 28% of cases.[195] The majority of lesions of the mandibular alveolus are located posterior to the canines, extension to the floor-of-mouth or buccal mucosa being common.[196]

Alveolar tumours are staged by their size until there is invasion of tumour through cortical bone into marrow space when the tumour becomes T4. Cervical lymphadenopathy is present in 24–32% of patients at presentation, usually to levels I and II,[195, 196, 198] with 15% of patients having occult metastasis.[196] Up to 94% of patients have evidence of bone involvement clinically.[198] Most tumours at this site are usually well or moderately differentiated.[196, 198]

Workup

The most important aspect of working up mandibular alveolar tumours is to determine the degree of bone involvement since this determines the extent of tumour resection.

Treatment

PRIMARY

Mandibular alveolar carcinoma is considered a surgical disease.[198] Invariably some degree of bone resection is required, 6–7% requiring soft tissue resection only.[196, 198, 199] Small alveolar carcinomas with no clinical evidence of significant bone involvement may be resected via a per oral approach with a marginal mandibulectomy, aiming for a 1 cm soft tissue and bony margin. Larger tumours with obvious bone involvement require segmental resection and extraoral access incisions. Segmental resection should be considered for tumours abutting a mandible previously exposed to radiotherapy, large soft tissue tumours adjacent to the mandible, involvement of the inferior dental nerve or intraosseous tumours (primary or secondary). Marginal mandibulectomy is preferable to segmental resection whenever oncologically acceptable. If a marginal resection is conducted then reconstruction may usually be achieved by primary closure. More extensive mucosal defects may require reconstruction with a skin graft; local flaps such as the FAMM flap, nasolabial flap or buccal fat pad; or microvascular free-tissue transfer to achieve acceptable soft-tissue closure. Segmental mandibular resection should be accompanied with composite microvascular free-flap reconstruction whenever feasible. Small, lateral mandibular defects may be reconstructed with a reconstruction plate and soft-tissue flap only, however central defects or larger lateral defects should be reconstructed with vascularized bone to minimize the risk of complications.[200] The use of a recognized mandibular defect classification helps surgeons plan appropriate reconstruction and communicate effectively with colleagues. The H, C, L, o, m, s classification system[201] accurately describes mandibular surgical defects.

NECK

Regional spread of mandibular alveolar tumours is usually to the ipsilateral level I–III nodes. END is indicated in tumours T2 in size or greater or any tumour with demonstrable bone invasion, clearance of levels I–III being adequate.[202] Lesions overlying the symphysis are thought to be associated with a higher risk of cervical metastasis and may require bilateral neck dissections. It has been argued that a staged neck dissection should be considered if histological examination of the primary tumour demonstrates bone involvement.[202] A more extensive neck dissection should be conducted in the presence of confirmed cervical metastasis, level V requiring treatment.[202]

PORT

Indications for PORT include positive margins (soft tissue or bone), multiple positive nodes or extracapsular spread.[196]

Recurrence

Recurrence rates for mandibular alveolar carcinoma at 2 years are 13–25%.[195, 196, 198] Higher recurrence rates are associated with increasing T stage[199] and positive resection margins.[195, 196]

Prognosis

Overall 5-year survival for lower alveolus carcinoma is 50–60%, disease-specific survival being 73–80%.[195, 196]

Cervical metastasis has been demonstrated to significantly reduce prognosis for lower gingival carcinoma.[202] Increasing T stage and particularly tumours greater than 3 cm,[196] bone involvement (cortical or cancellous),[196] positive resection margins[195, 196] are associated with decreased prognosis.

Tooth extraction at the site of primary tumour does not influence prognosis.[195, 196]

KEY POINTS

- Represents approximately 10% of oral cancers, although up to 30% in the Japanese population.
- 94% of tumours involve bone.
- Alveolar carcinoma is a surgical disease requiring a rim or segmental resection of the mandible.

MANAGEMENT OF THE MANDIBLE

Tumours of the mandibular alveolus, the floor of mouth, buccal mucosa or retromolar trigone may involve the bone of the mandible. Involvement of the mandible has

significant consequences regarding management of the patient.

Squamous cell carcinoma invades the mandible either in an invasive or erosive manner.[199, 203] Invasive tumours demonstrate fingers or islands of tumour advancing deeply into bone with no obvious osteoclastic activity. Erosive tumours have a broad advancing front with osteoclast activity and connective tissue between the tumour and bone, although as the depth of invasion increases they may become more invasive in character. Large, deeply invading tumours are more likely to demonstrate an invasive pattern of spread and involve the mandible.[199, 204]

Tumours enter the mandible at the point of contact,[199, 205] usually the junction of the attached and reflected mucosa, whether the patent is edentulous or dentate. The mandible should be considered at risk at any point where tumour is in contact and this taken into account when planning resection.[206] Clinical fixation of the tumour to bone is not necessary for bone invasion to occur.

It has been demonstrated that it is primarily the size and extent of the tumour that dictates the pattern of spread once in bone rather than anatomical features such as the inferior alveolar nerve or periodontal ligament. Preferential spread within the mandible via the inferior alveolar nerve or medullary space is rare,[199, 207] justifying 1 cm margins.

Tumours demonstrating an invasive pattern of spread are more likely to give rise to cervical metastasis with extracapsular extension,[199] an indication of their more aggressive nature. Pre-operative imaging of the mandible is necessary to determine if bone resection is required, and if so the appropriate type of resection.[208]

At present there is no single investigation that can reliably predict bone invasion. An OPG radiograph should be requested for all cancer patients. This plain radiograph is not only useful for demonstrating bony invasion but also for assessing mandibular height, dental anatomy and dental pathology. It should be remembered that plain X-rays do not detect initial invasion until 30% demineralization has occurred, giving rise to reduced sensitivity.[209] Clinical examination and OPG alone are inadequate for accurate assessment of mandibular invasion.[209]

Axial MRI views with T1 and Short-TI Inversion Recovery (STIR) fat suppression are very sensitive for imaging the primary site of oral cancer with an adequate specificity.[210] Bone scintigraphy or single photon emission computed tomography (SPECT) may be considered in equivocal cases, SPECT being demonstrated to have up to 100% sensitivity in determining bone invasion.[211] When bone involvement is equivocal on pre-operative imaging then periosteal stripping looking for cortical bone disruption at the time of resection may help the clinician plan the resection.

A rim resection/ marginal mandibulectomy should be considered for T1/2 tumours with early invasion (< 5 mm) and adequate bone height of the mandible (dependant on pre-operative imaging, clinical examination and periosteal stripping).[212, 213] Traditionally rim resections have been conducted horizontally, however, with the understanding that tumour may enter the mandible at any point of contact it becomes apparent that the saw cut should be angled to accommodate this.[199] Marginal resections in the retromolar region may include the coronoid process. Every effort should be made to preserve the inferior alveolar neurovascular bundle when conducting a marginal resection in an edentulous mandible so as to minimize the risk of avascular necrosis and iatrogenic fracture. The anterior and posterior margins of a rim resection should be curved so as to minimize the risk of iatrogenic mandibular fracture. Rounding of the edges of the rim resection also minimizes the risk of bone exposure[214] and minimizes the risk of trauma to the pedicle of a microvascular free flap if used for soft tissue reconstruction. If the depth of the mandible following rim resection is less than 10 mm then consideration should be given to converting the resection to a segmental resection.

Segmental mandibular resection and composite reconstruction should be conducted for extensive mandibular invasion or deeply invading soft-tissue tumours that abut the whole depth of mandible. Segmental resection should also be considered in the previously irradiated mandible.[215, 216] The surgeon should aim for a 1 cm margin of the soft tissue tumour, it being highly unusual to get a positive bone margin in the absence of a positive soft-tissue margin.[212]

Usually intra-operative assessment of bony margins is not conducted, however techniques for frozen section analysis of cancellous and cortical bone have been described.[217]

If the planned resection of mandible follows the guidelines set out above then long-term prognosis and recurrence does not differ between marginal resection and segmental resection.[218, 219] The presence of bone involvement, rather than the depth of bone invasion, is the main determining factor of long-term prognosis.[196, 220] It has been proposed that only tumours with an invasive tumour front as opposed to an erosive front be classified as T4 tumours.[220] It is thought that local recurrence following bony resection is usually as a consequence of soft-tissue margin status rather than method of mandibular resection.[221]

Rim resection of the mandible maintains bony continuity and hence is usually associated with an excellent functional and cosmetic outcome. The rim resection in addition to maintaining the structural integrity of the mandible also usually preserves sensation of the lower lip and muscular attachments. With modern reconstructive techniques the Andy Gump deformity should no longer be encountered. Patients' quality of life following mandibular resection is influenced by many factors such as site of bony resection, type of bony resection, the soft-tissue resection, type of reconstruction, adjunctive radiotherapy etc.

It is recognized that whenever oncologically sound, a rim resection should be the resection of choice.[222] However, it has been demonstrated that there is little or no difference in quality of life between a rim resection and segmental resection with composite microvascular free tissue transfer,[226] particularly when the resection is greater than 4 cm.[223]

KEY POINTS

- Bone involvement may be by erosion or invasion.
- Bone involvement occurs at any point where tumour contacts bone.
- MRI, CT, SPECT and periosteal stripping are complimentary in assessing bone involvement.
- Bone margins should be dictated by overlying soft-tissue margins.
- Rim resection should be conducted when oncologically acceptable.

LIP RECONSTRUCTION

Omar A. Ahmed

INTRODUCTION

The lips are complex, highly specialized structures, which are the most mobile elements of the lower third of the face. They serve a critical, aesthetic and functional purpose, which cannot be replicated by any other tissue. Hence it is imperative, wherever possible, to replace lip defects with lip tissue.

The lips are considered to be the beginning of the oral cavity, and they form a fleshy, sensate, highly mobile partition, which separates the intraoral contents from the exterior. They are thus responsible for oral continence, but also play an important role in eating, swallowing, speech, and both verbal and non-verbal communication.

ANATOMY

The lips surround the oral cavity. They are composed externally of skin and internally of mucous membrane. The lips extend from the nose superiorly to the chin inferiorly, and are bound laterally by the nasolabial folds. It is important to have a good knowledge of the anatomical landmarks of the lips (**Figure 12.5**).

The external landmarks of the upper lip are the philtral columns, the Cupid's bow, and the white roll. The philtral columns are a pair of near-vertical ridges, extending from the nasal columella to the vermilion border, which are formed by the underlying orbicularis oris muscles. The philtral columns merge caudally with the white roll, another ridge formed by the orbicularis oris muscle. The philtral dimple is a depression in the central lip between the philtral columns. The Cupid's bow is the curved part of the white roll between the bases of the philtral columns. The main external landmark of the lower lip is the white roll.

A cross-section of the lips reveals the following structures from external to internal: skin and vermilion, subcutaneous tissue, muscle, submucous glands and mucosa (**Figure 12.6**).

The skin of the lips is hair-bearing, with the hair being mostly vellus in women and children. It is rich in sebaceous and sweat glands. Deep to the skin is a significant amount of subcutaneous fat that makes up the bulk of lip thickness. The vermilion extends from the white roll to the wet-dry border, beyond which it transforms into mucosa. It is important to understand the distinction between the vermilion and the mucosa. The vermilion is stratified squamous epithelium with a thin layer of surface keratin. It contains no glands, and is dryer and duller in appearance than mucosa. Mucosa is non-keratinized epithelium that is rich in minor salivary glands and lines the inside of the lip.

The perioral musculature can be classified into three groups based on their attachments (**Figure 12.7**). Group I muscles attach to the modiolus, which is a tendinous thickening at each oral commissure. Group II muscles insert into the upper lip, and Group III muscles insert into the lower lip. Group I muscles include the orbicularis oris, buccinator, levator anguli oris, depressor anguli oris, zygomaticus major and risorius. Group II muscles include the levator labii superioris, levator labii superioris alaeque nasi and zygomaticus minor.

Group III muscles are the depressor labii inferioris, mentalis and platysma.

The paired orbicularis oris muscles are the sphincter muscles of the lips and are essential for oral competence. They also evert and protrude the lips, as in pouting and kissing. They originate at the modiolus, just lateral to the oral commissure. The two muscles insert into a midline raphe in the lower lip, but in the upper lip they cross

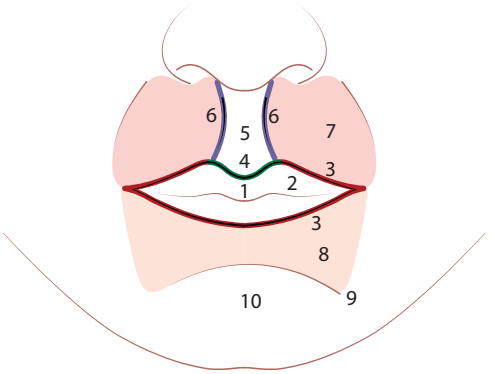


Figure 12.5 Subunits of the lip. 1. Tubercle. 2. Vermilion. 3. Vermilion border. 4. Cupid's bow. 5. Philtrum. 6. Philtral columns. 7. Cutaneous upper lip. 8. Cutaneous lower lip. 9. Labiomental sulcus. 10. Chin.

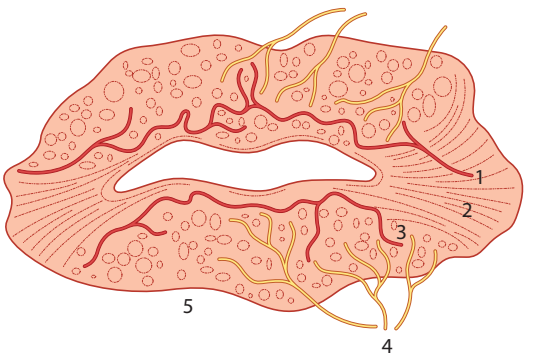


Figure 12.6 Coronal cross-section through lips. 1. Superior labial artery. 2. Muscle fibres. 3. Inferior labial artery. 4. Sensory nerve supply from the infraorbital nerve and motor supply from the lower buccal and mandibular branches of the facial nerve. 5. Fat and subcutaneous tissue.

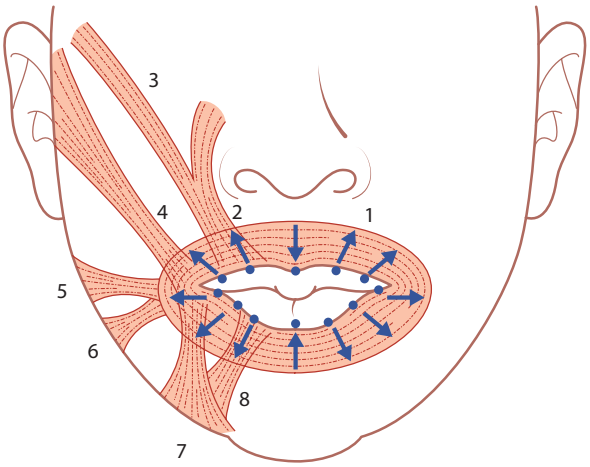


Figure 12.7 Key perioral muscles. Arrows show direction of pull on the lips. 1. Orbicularis oris 2. Levator superioris 3. Zygomaticus minor 4. Zygomaticus major 5. Risorius 6. Buccinator 7. Depressor anguli oris 8. Depressor labii inferioris.

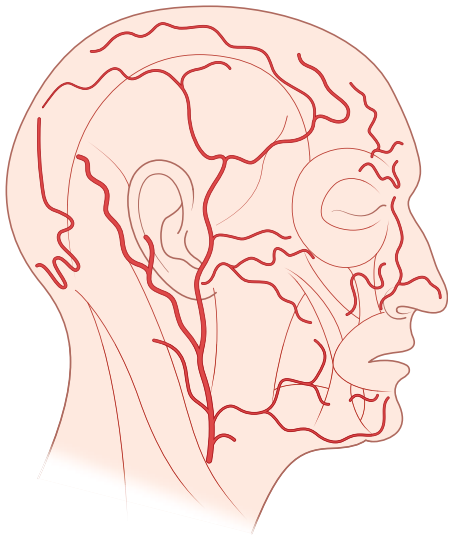


Figure 12.8 Major blood supply to the face.

the midline to insert into the contralateral philtral column. The orbicularis muscles are innervated by buccal branches of the facial nerve. The second most important lip muscles are the paired mentalis muscles, which are the primary elevators of the lower lip. They maintain the lower lip in a correct position at rest, and help maintain oral competence by pushing the lower lip against the upper lip. The mentalis muscles are large trapezoidal muscles that attach superiorly to the mandible just below the attached gingiva and inferiorly to the chin pad below the labiomental sulcus. Each muscle is innervated by the corresponding marginal mandibular branch of the facial nerve.

The depressors of the lip are the depressor anguli oris and the depressor labii inferioris, innervated by the marginal mandibular branch of the facial nerve, and the platysma, whose nerve supply is from the cervical branches of the facial nerve. The elevators of the upper lip include the levator labii superioris, zygomaticus major and minor, and levator anguli oris, which lift the central upper lip, lateral upper lip and commissure respectively. These muscles are innervated by the zygomatic and buccal branches of the facial nerve.

The sensory innervation of the lip is provided by the infraorbital and mental nerves. The infraorbital nerve is a branch of the maxillary division of the trigeminal nerve, which enters the face through the infraorbital foramen and provides sensation to the nasal sidewall, nasal ala and the upper lip. The mental nerve is a branch of the posterior trunk of the inferior alveolar nerve, which arises from the mandibular division of the trigeminal nerve. The mental nerve exits the mandible between the first and second premolar teeth. It provides sensation to the lower lip. Intraoral infiltration of small amounts of local anaesthetic solution around the bony exit points of these two nerves allows for rapid and complete anaesthesia of the lips, making it easy to perform surgical procedures without general anaesthesia.

The lips have a rich vascular supply (**Figure 12.8**). The arterial supply is from the superior and inferior labial arteries, which are branches of the facial artery. Each labial artery communicates with its counterpart across the lip, forming a continuous arterial circle around the oral sphincter. This allows for considerable versatility in local flap design. The arteries lie at the wet-dry border, just deep to the orbicularis oris muscle, and send numerous perforators through the orbicularis muscle to the overlying skin. The blood supply to the labial skin is so rich that local flaps can survive even when they do not include a labial artery. The venous drainage of the lips is more unpredictable than the arterial supply. The labial veins can drain into the anterior facial veins, transverse cervical veins, the superficial temporal veins and the submental veins.

Knowledge of the lymphatic drainage of the lips is important for oncological considerations. Drainage from the upper lip is primarily to the submandibular nodes, but the commissure can drain to the periparotid nodes. Both of these nodal regions subsequently drain to the jugulodigastric nodes. The drainage is mostly to ipsilateral nodes, although the midline of the upper lip can also drain to contralateral nodes. The lower lip also drains to the ipsilateral submandibular nodes with the exception of the midline lip, which drains into the submental nodes. Drainage from the central lower lip frequently crosses the midline. The submental nodes subsequently drain into the submandibular nodes.

HISTORY OF LIP RECONSTRUCTION

A wide variety of techniques have been described to reconstruct the lips. Functional and aesthetic results are best when the lip tissues are oriented in their correct anatomical positions.

Lip reconstruction has been practised for centuries, and most modern techniques are based on older techniques. Sushruta, the great Indian physician and surgeon, provided one of the earliest written records of lip reconstruction in his compendium of surgery (*Sushruta Samhita*), possibly around 600 BC.[228] The Roman

physician Celsus is credited with the original description of the classic wedge excision and primary closure of the lip in the 1st century AD. The Branca family and, later, Tagliacozzi popularized staged tissue transfer techniques in the late 16th century. Tagliacozzi is also credited with writing the first textbook on plastic surgery. In 1818, von Graefe described lip reconstruction in the second textbook on plastic surgery, and was the first to coin the term 'plastic surgery'. Shortly thereafter, in 1834, Dieffenbach described the first cheek advancement flap techniques.[229] The Italian surgeon Pietro Sabattini (1838) came up with the concept of lip-switch flaps,[230] which were popularized in the late 19th century by Abbe[231] and Estlander[232] and are still in common use. In 1853, von Burow[233] applied his principle of skin triangle excisions to facilitate advancement to bilateral cheek advancement flaps for total lip reconstruction. Bernard[234] described a similar technique in 1852. Modifications of the von Burow and Bernard techniques remain useful to this day, especially that of Freeman[235] (1958) and Webster[236] (1960). In the 1920s Gillies introduced the fan flap, which was aimed at restoring a competent oral sphincter. Karapandzic[237] described his elegant neurovascular lip rotation technique for large defects in 1974. Harii and Ohmori were the first to use microvascular free tissue transfer for extensive defects of the lip (1975).[238]

AETIOLOGY OF LIP DEFECTS

The majority of lip defects requiring reconstruction arise from tumours or trauma. Lip tumours can be congenital or acquired. Haemangiomas and vascular malformations are common congenital tumours. Skin cancers make up the bulk of acquired tumours. Basal cell carcinomas tend to occur in the upper lip and squamous cell carcinomas in the more sun-exposed lower lip. Both of these tumours are more common in the elderly. Malignant melanomas also often occur in the lips and can occur at any age. Traumatic lip defects usually occur in young, healthy patients.

PRINCIPLES OF LIP RECONSTRUCTION

1. In order to maintain oral continence, an attempt should always be made to preserve the nerve supply to the reconstructed lip.
2. Muscle-carrying lip vermilion is precious tissue and should also be preserved.
3. Lip tissue should preferentially be used to reconstruct the lip.
4. Whenever possible the muscles of the lip should be correctly orientated.
5. When a lip defect is too large to be reconstructed by remaining lip tissue, adjacent tissues such as the cheeks should be used.
6. Reconstruction by distant tissues, such as free-tissue transfer, should only be performed when there is insufficient local tissue to reconstruct the defect.

Reconstruction of the vermilion

Scars within the vermilion usually heal extremely well. Small vermilion defects can often be closed directly. Lateral superficial defects can be allowed to heal by secondary intention, as long as they are not too close to the white roll. Larger vermilion defects that do not involve the white roll require flap reconstruction, either lip (vermilion) flaps or non-lip (mucosal and tongue) flaps.

Vermilion flaps are best suited for defects close to the white roll and include vermilion advancement flaps or vermilion 'switch' flaps from the opposite lip. Vermilion advancement flaps are reliable flaps based on the labial vessel. The external incision is made directly on the vermilion border and the mucosal incision is made at the corresponding level inside the lip. In vermilion switch flaps the vermilion is cut in similar fashion to a vermilion advancement, but the flap is inset to the opposite lip. If only part of the vermilion is used, the secondary defect is closed directly at the time of inset. If, on the other hand, the full height of the vermilion is used, the defect in the donor lip is reconstructed by vermilion advancement at the time of flap division.

Mucosal advancement flaps are useful for total vermilionectomy defects after cancer resection. In such situations, it is important to carefully raise the mucosal flap in the plane between submucosa and muscle so as to maximize sensory innervation of the reconstructed vermilion. When a lip 'shave' has been performed for dysplasia, resulting in a shallow defect of vermilion, mucosa can be sutured directly to the skin without undermining. Mucosal advancement is also indicated for broad defects that are remote from the vermilion border. These flaps can be raised in V-Y fashion or as bipedicled flaps.

When mucosa is insufficient, tongue flaps can be used. They are usually raised on the lateral border of the tongue and can be anteriorly or dorsally based for vermilion reconstruction. The anteriorly based lateral tongue flap provides more bulk than the dorsally based flap. Tongue flaps are performed in two stages and are best reserved for lateral vermilion defects.

Reconstruction of the upper lip

Superficial defects of the upper lip, with intact orbicularis oris, can often be reconstructed by simple methods. Central defects involving less than half the distance between the philtral columns can either be repaired primarily or with a wedge resection. In all wedge resections, it is essential that the orbicularis muscle be accurately repaired for normal lip movement. If the defect is superficial and involves more than half of the central lip without crossing the philtrum, a full-thickness skin graft can give adequate results. In men, this graft could be taken from hair-bearing preauricular skin to restore hair growth. For superficial lateral defects which are less than half the width of the

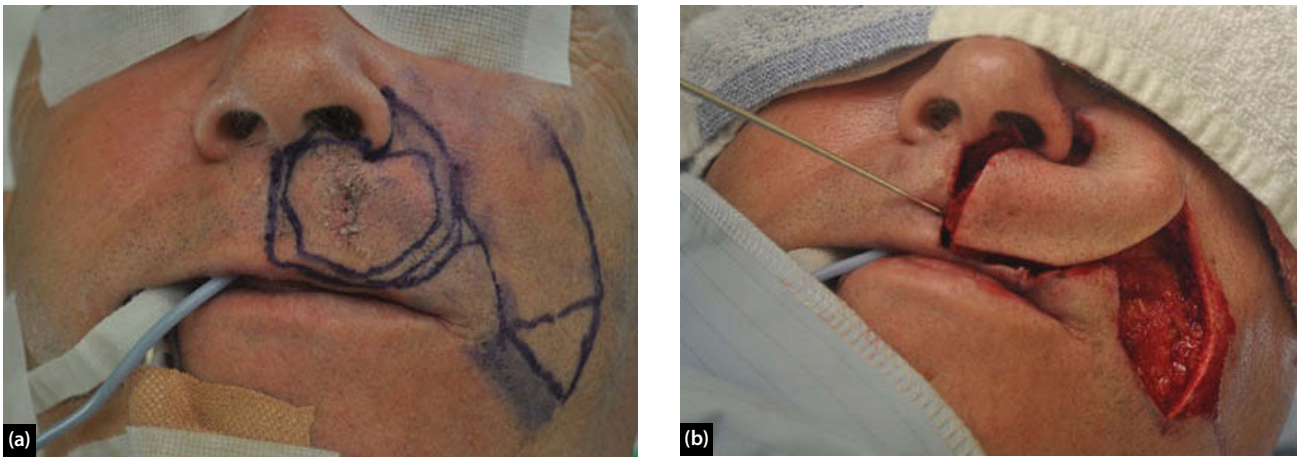


Figure 12.9 (a) Upper lip cancer prior to excision, showing design of a superiorly-based hair-bearing nasolabial flap from left cheek. **(b)** Nasolabial flap being transposed to defect.

lateral lip, wedge resection is a good option. When the defect involves more than half the width of the lateral lip, a local flap from the cheek may be a good option (**Figure 12.9**). Alternatively, a full-thickness graft can be just as acceptable.

The management of full-thickness defects of the upper lip depends on their size and location. Defects up to one-third in width can usually be closed directly, often with the aid of perialar crescentic excisions.[239] If primary closure is employed for central defects it can result in a narrow central lip, but this is usually cosmetically acceptable. When a central defect is greater than half of the upper lip, an Abbe-Sabattini flap from the lower lip is indicated (**Figure 12.10**).

In such situations the whole central lip subunit (from philtral column to philtral column) should be excised. The width and height of the flap should equal that of the upper lip defect. The flap is based on a single inferior labial artery and should ideally be harvested from the central lower lip. It should include the central raphe of the orbicularis oris muscles. When raising the flap, all elements of the lower lip are divided on the non-pedicle side, making a note of the location of the labial artery. On the pedicle side, the artery and a small cuff of mucosa are preserved. The donor defect on the lower lip is generally closed primarily before the flap is inset in layers to the upper lip and columella. The pedicle can be safely divided at 2–3 weeks. This flap is ideal for secondary correction of bilateral cleft lips when there is inadequate upper lip height and volume. A major disadvantage is the two stages required for transfer.

The Abbe-Sabattini flap can also be used to replace lateral lip defects larger than a third if the defect does not involve the oral commissure. If the lip switch flap is combined with perialar crescentic excision and lip advancement, this narrows the lateral upper lip defect so that a smaller flap is required from the lower lip.

For defects of the upper lip greater than 50%, a larger lip switch flap can be used in combination with bilateral perialar crescentic excision and advancement. The large lower lip donor defect can then be closed with the aid of bilateral Schuchardt medial advancement (**Figure 12.11**).

This technique will create microstomia which may require secondary revision. When performing lip-sharing procedures, it is important to maintain a balance between upper and lower lip length.

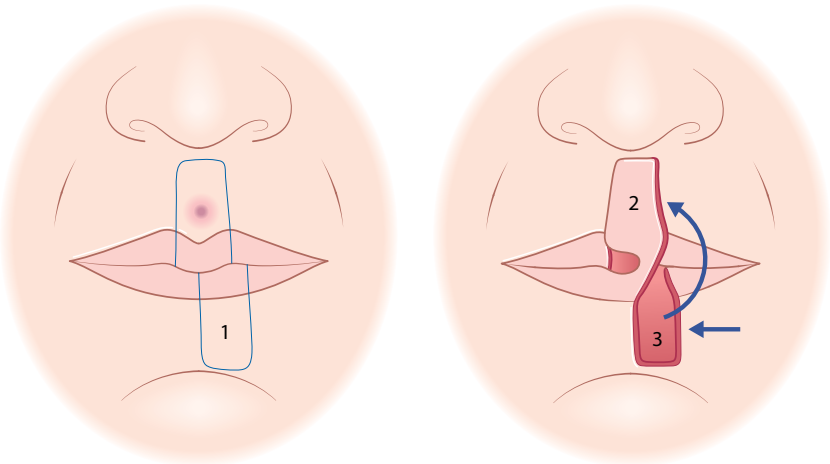


Figure 12.10 Abbe-Sabattini flap. 1. Design of flap and subunit excision. 2. Rotate the flap into the defect on its pedicle. 3. Close the donor site.

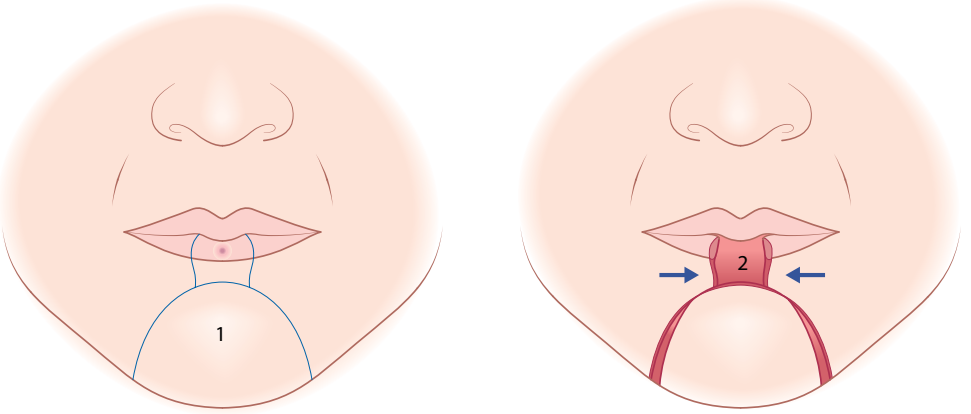


Figure 12.11 Schuchardt bilateral medial advancement flap.
1. Design the full thickness excision and the submental triangles for excision. 2. Advance the lower lip and chin to close the defect.

Subtotal and total upper lip defects are, thankfully, rare and reconstruction with local tissues may not be possible. Fortunately, the upper lip is not as important for oral competence as the lower lip, and static reconstruction with a folded soft-tissue flap, such as a radial forearm free flap, can provide a reasonable total upper lip reconstruction in a single stage.

Reconstruction of the lower lip

Superficial defects of the lower lip are usually best treated by full thickness wedge excision and primary closure, though extensive superficial defects may be simply reconstructed by a full-thickness skin graft, especially if the bulk of lip muscle is still present.

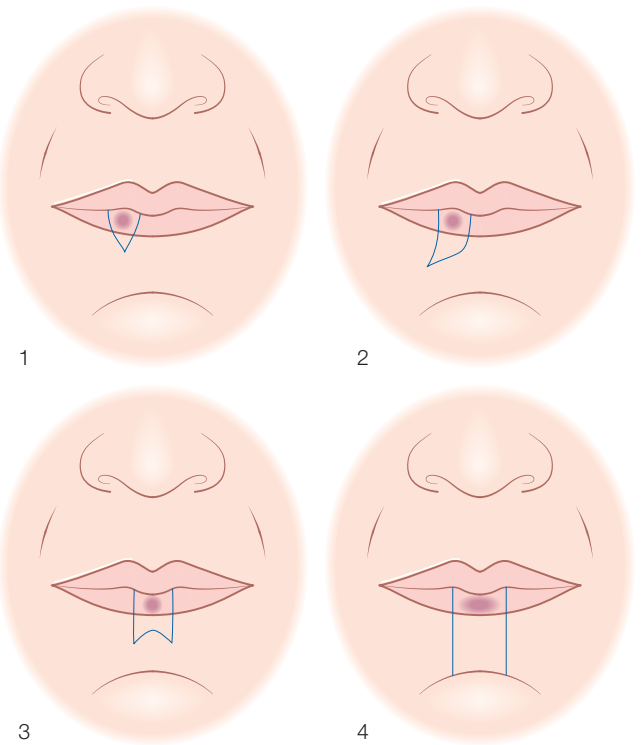


Figure 12.12 Greater than 1/3 lower lip defects closed with (1–3) various wedge techniques or (4) bilateral advancement flap-similar to the Schuchardt reconstruction (see Figure 12.10).

Techniques to reconstruct full-thickness defects of the lower lip can be conveniently classified into three groups, depending upon the size of the lip defect:

1. Defects of up to one-third of the lip width.
2. Defects of between one-third and half of the lip width.
3. Defects greater than half of the lip width.

DEFECTS OF UP TO ONE-THIRD OF THE LIP WIDTH

In the vast majority of cases, up to one-third of the lower lip can be removed by simple wedge excision (**Figure 12.12**) and the resultant defect is then closed primarily in layers. In elderly patients, with greater tissue laxity, this is never a problem (**Figures 12.13a** and **12.13b**).

In a minority of cases the wedge may have to be modified, by extending the incision unilaterally or bilaterally along the labiomental fold and excising skin crescents. This aids in advancing the remaining lip centrally. When the crescents are bilaterally extended as far as the mandibular border, accompanied by mucosal release incisions, this is known as the Schuchardt procedure.

DEFECTS OF BETWEEN ONE-THIRD AND HALF OF THE LIP WIDTH

Rarely, in some elderly patients with lax tissues, it may be possible to primarily close wedge excisions greater than one-third of the width of the lower lip. In the vast majority of cases, however, reconstruction of between one-third and half of the lower lip is best performed by using residual lip tissues, or lip sharing. Lip-sharing techniques preserve lip function and have satisfactory aesthetic results but can cause microstomia.

The Karapandzic technique[237]

This is arguably the best method to reconstruct lower lip defects which cannot be directly closed. This rotation-advancement technique can be used on both lateral and central lower lip (and sometimes upper lip) defects. A unilateral flap can suffice in lateral defects, but for central defects bilateral flaps are required.

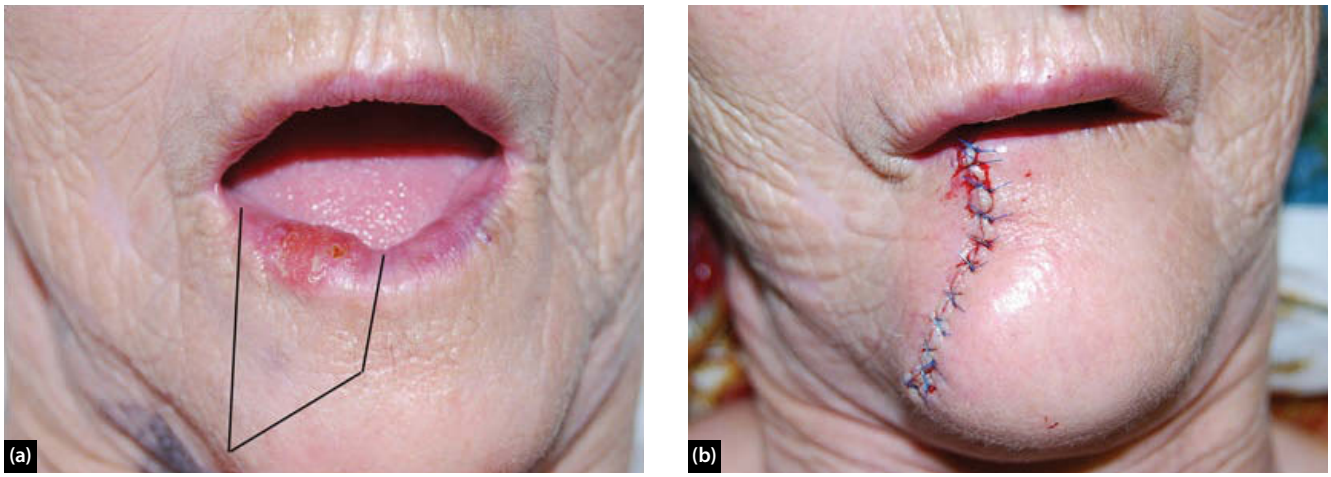


Figure 12.13 **(a)** Modified wedge excision of lower lip squamous cell carcinoma in an elderly patient. **(b)** Closure of wedge excision.

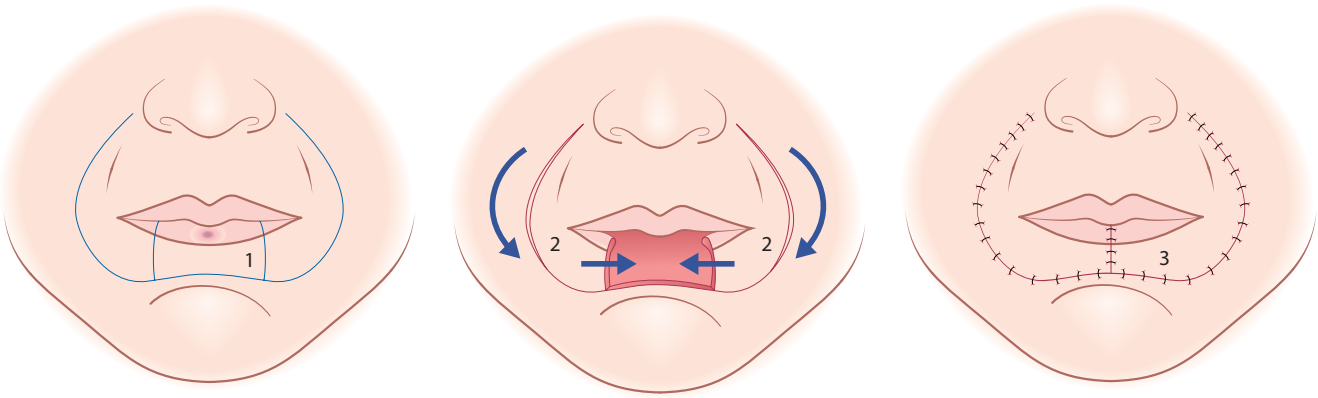


Figure 12.14 Karapandzic technique: 1: Mark out the excision margin and flap. The flap should be the same height as the lip at all points around the flap. 2: After full thickness excision including mucosa, mobilize the crescenteric flaps at equidistance from the free lip margin and full thickness for 2 cm from the postexcisional defect. With scissors the blood and nerve supply around the commissure is preserved. 3: Tension-free rotation of the flaps recreate the lower lip and vermilion.

The Karapandzic technique creates paired full-thickness mucomusculocutaneous lip flaps supplied by branches of the facial artery and preserves the sensory and motor nerves to the lip segment (**Figure 12.14**). It is crucial that the skin incisions are made at a distance from the lip margin equivalent to the height of the lip defect, especially at the commissures, in order to restore normal lip height. It should be noted that the superior incisions are normally placed lateral to the nasolabial creases for this purpose. The mucosal incisions are parallel to the skin incisions but are much shorter: usually about 2 cm on each side. For central lower lip defects, the lip depressor muscles have to be completely divided bilaterally to allow the flaps to move medially. For large defects, the superior incisions are deepened through skin, fat and the superficial layer of facial muscles, with the buccinator and orbicularis oris being preserved. During this manoeuvre, the delicate vessels and nerves to the lip must be carefully preserved. It is important to note that the nerves enter the flaps radially. After flap rotation the superficial muscle layer should be reattached to the orbicularis. For relatively small defects, it is possible to rotate the flaps without necessarily dividing the superficial facial muscles; instead the muscles in the superior incisions can simply be teased or stretched until the flaps are free to advance- the 'cut as you go' approach. After flap rotation, the wounds are closed in layers from within outwards, paying careful attention to the muscle layer. The functional results of this reconstruction are very good, but microstomia is inevitable with large defects (**Figure 12.15**).

Johanson's step technique[240]

This method of lip advancement can only be applied to lower lip defects. The lip lesion is removed as a rectangle and the remaining lateral lower lip segments are advanced medially. To aid this advancement, square or rectangular segments of skin and subcutaneous tissue lateral to the defect are excised in a descending stepwise fashion along the labiomental crease, until advancement of the lateral lip flaps can take place without tension. Each segment excised is approximately half the width of the lower lip resectional defect. The final (caudal) segment to be excised

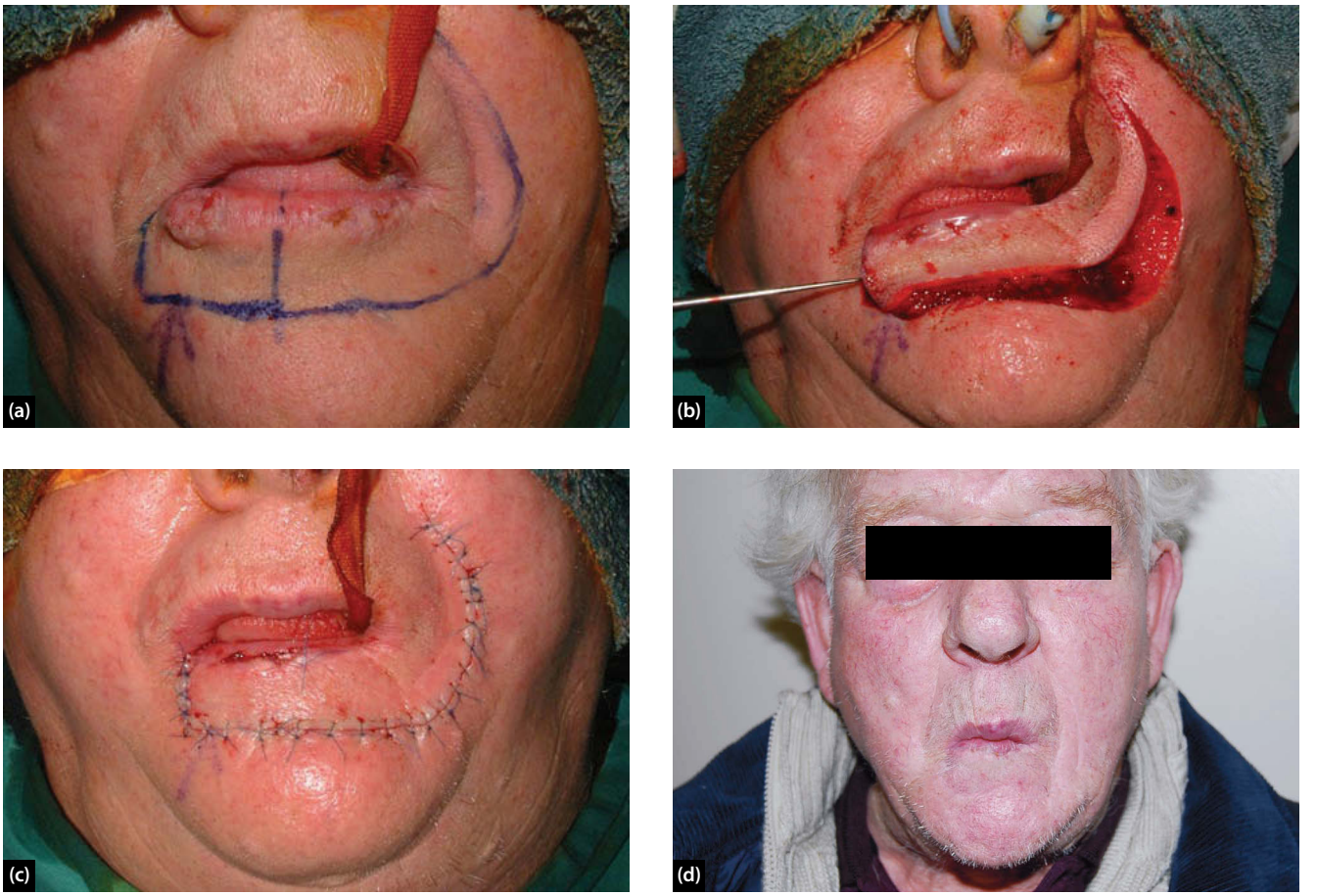


Figure 12.15 **(a)** Markings for resection of squamous carcinoma of right side lower lip and design of contralateral Karapandzic flap. **(b)** Karapandzic flap assessed for adequate mobilization. **(c)** Karapandzic flap inset. **(d)** Good aesthetic and functional result.

is triangular in shape. As the flaps advance medially, the 'steps' are closed (**Figure 12.16**). The lip should then be closed in layers, with careful reconstruction of the orbicularis. The functional results of this technique are comparable to that of Karapandzic, but the scar can appear unnatural. Reconstruction of larger defects will lead to microstomia.

Lip switch flaps

Defects of the lower lip not involving the commissure can be reconstructed by an Abbe-Sabattini flap from the upper lip (**Figure 12.17**). The flap should be half the width of the lip defect, in order to avoid excess shortening of the upper lip and to evenly distribute tissues between the upper and lower lips.

These flaps lead to an insensate, adynamic segment of lip, and, though a degree of reinnervation eventually occurs, are better suited for upper lip reconstruction. Their main advantage is that they do not blunt the oral commissures.

Defects close to the commissure can be reconstructed in a single stage by the Estlander flap (**Figure 12.18**). This technique is similar to the Abbe-Sabattini flap but reconstructs the oral commissure, though the new commissure is blunted.

The functional results of lip switch flaps are satisfactory, but not comparable to the Karapandzic or Johanson techniques.

DEFECTS GREATER THAN HALF OF THE LIP WIDTH

For larger defects, lip-sharing procedures such as the Karapandzic lip reconstruction can be used when tissue laxity allows (**Figure 12.19**). This preserves lip function, but a degree of microstomia will inevitably occur and secondary revision will usually be required. When the lip defect is greater than three-quarters, in the majority of cases there will be insufficient lip tissue for a satisfactory reconstruction. In such cases, the next best option is to use adjacent tissues. Such reconstructions can achieve satisfactory aesthetic results, but function is always suboptimal.

The Freeman modification of the Bernard-von Burow procedure

The Bernard-von Burow procedure reconstructs the lower lip by medially advancing the cheeks (**Figure 12.20**). Cheek advancement is facilitated by the excision of full-thickness

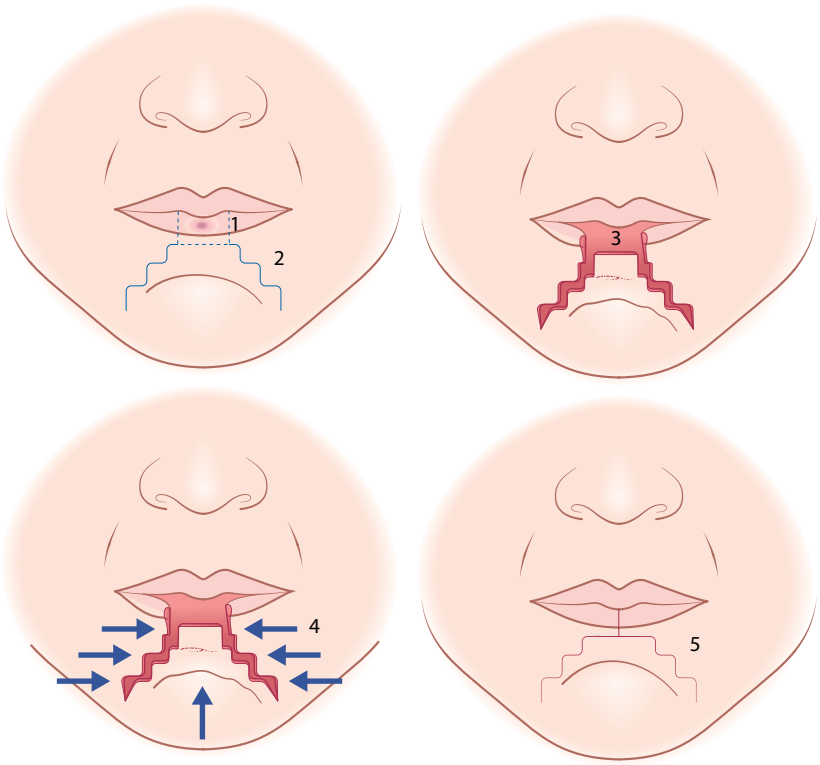


Figure 12.16 Johanson step technique for central defects of the lower lip. 1. Mark out the lesion. 2. Plan the step incision around the labiomental sulcus/chin subunit. 3. Full thickness excision of lesion and incise the step reconstruction full thickness. 4. Bring the medial lip excision margins together and advance the step flaps. 5. Closure.

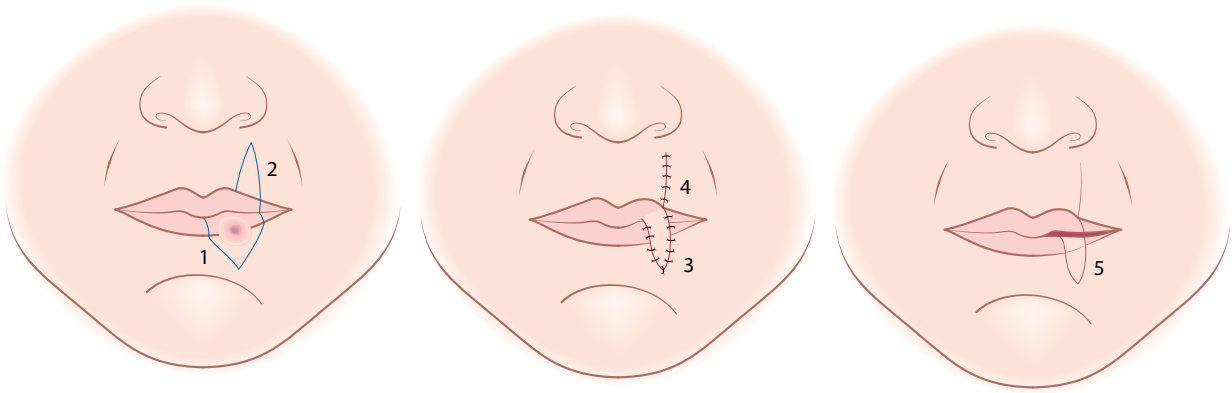


Figure 12.17 Reversed Abbe-Sabattini Flap to one-third lower lip lesion. 1. Lesion marked out for excision 2. Flap design; 3. Full thickness incision of the upper lip flap with the medial free margin of the upper lip inserted in the lateral margin of the lower lip excision. 4. Donor site closure. 5. The medial pedicle is divided and inset at 7 days.

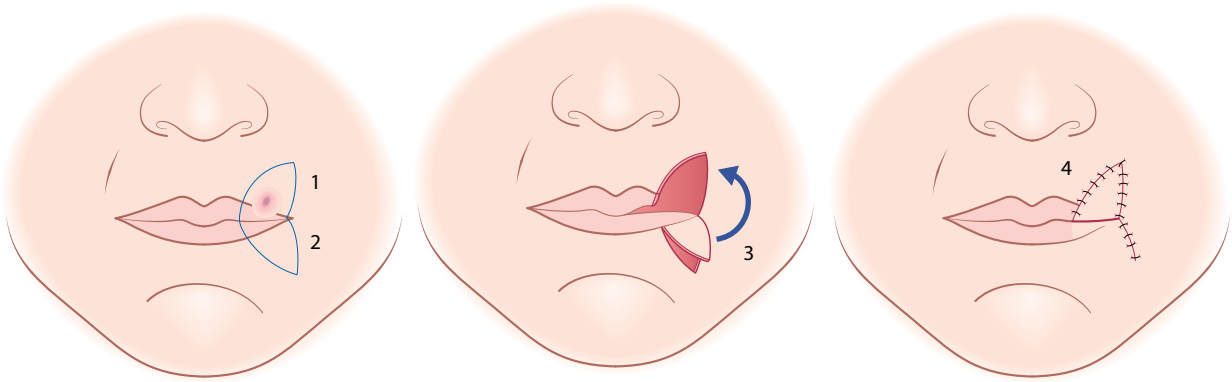


Figure 12.18 Abbe-Estlander Flap for partial commissure reconstruction: 1. Lesion marked out. 2. Corresponding flap marked to allow the medial lower lip pedicle to become the new commissure. 3. Rotate the flap into the defect. 4: Inset and closure of donor site.

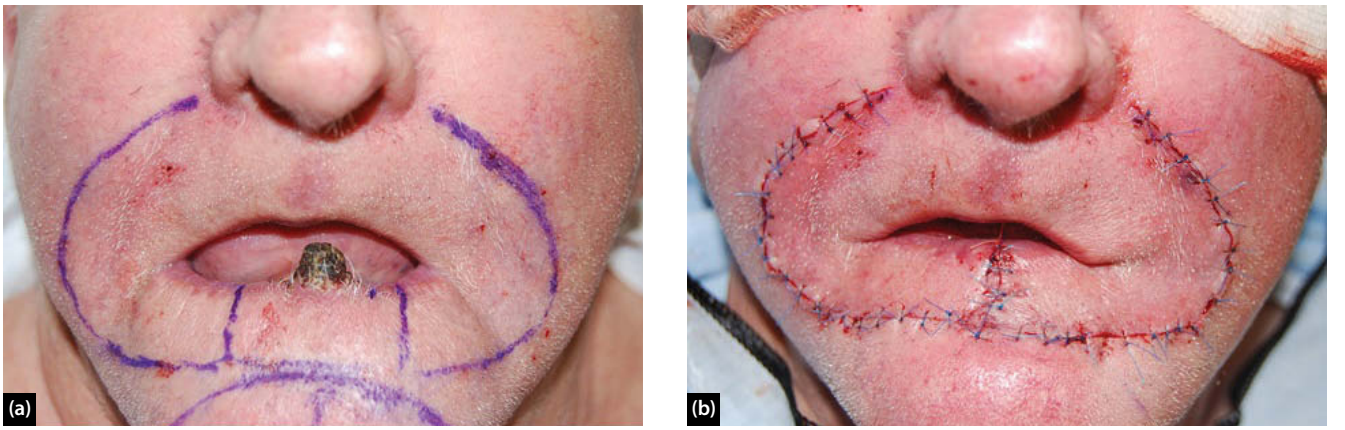


Figure 12.19 **(a)** Melanoma of central lower lip and design of bilateral Karapandzic flaps. **(b)** Bilateral Karapandzic flaps inset.

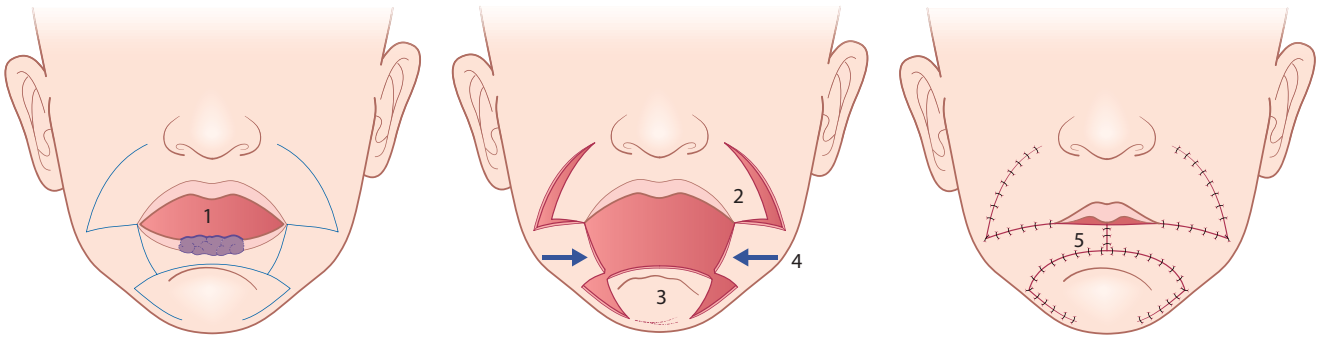


Figure 12.20 Modified Bernard-von Burow technique for up to total lip reconstruction. 1. Lesion marked out and flap with two superior and two inferior Burow's triangles marked out. 2. Burow's triangles are excised into subcutaneous tissue lateral to nasolabial folds. 3. Around the labiomental fold Burow's triangles are excised to allow medial rotation of the lower cheek flaps. 4. Medial advancement of the cheek flaps. 5. 3-layered closure of the midline with a mucosal flap reconstruction of the vermilion.

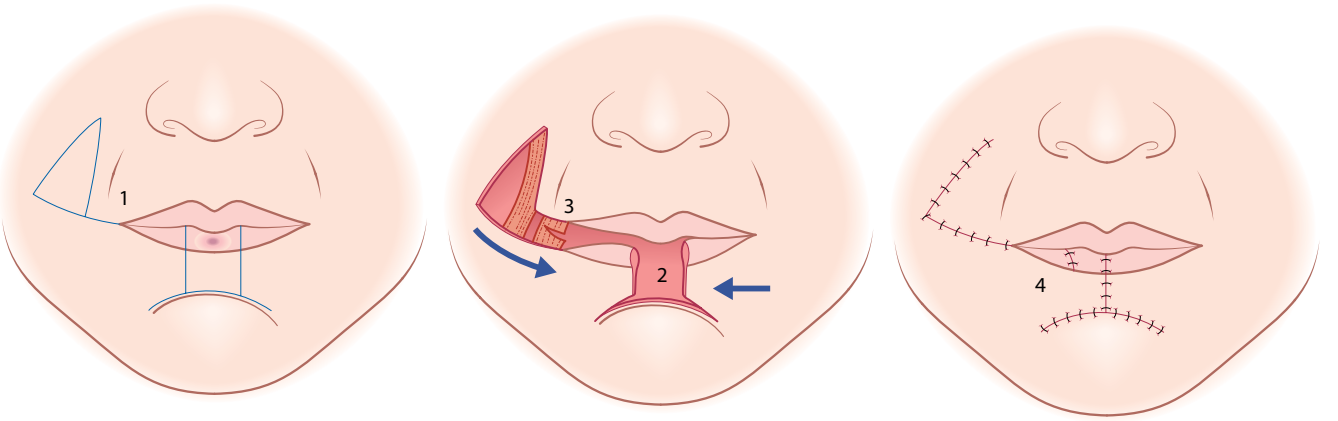


Figure 12.21 Unilateral Freeman modification of the Bernard-von Burow procedure. 1. Mark out excision margin and lateral nasolabial triangle. 2. Advance lower lip into defect. 3. Excision of tissue superficial to the muscle will allow lateral advancement whilst incision of the muscle lateral to the commissure will facilitate a commissuroplasty.

triangles of cheek tissue above and below the defect at the nasolabial fold. The width of the triangular excision is equal to the width of the defect. When both cheeks are advanced, the base of each triangle is half the width of the lip defect. The vermilion is reconstructed by tongue flaps. Webster's modification of this technique mobilizes cheek mucosa to reconstruct the vermilion.

The Freeman modification of the Bernard-von Burow operation is probably the best current cheek advancement technique (**Figure 12.21**).

Freeman converted the lower incision of the Bernard-von Burow operation from a horizontal one to a curved one, following the natural junction between the lip and chin. Only skin and fat is removed in the triangular

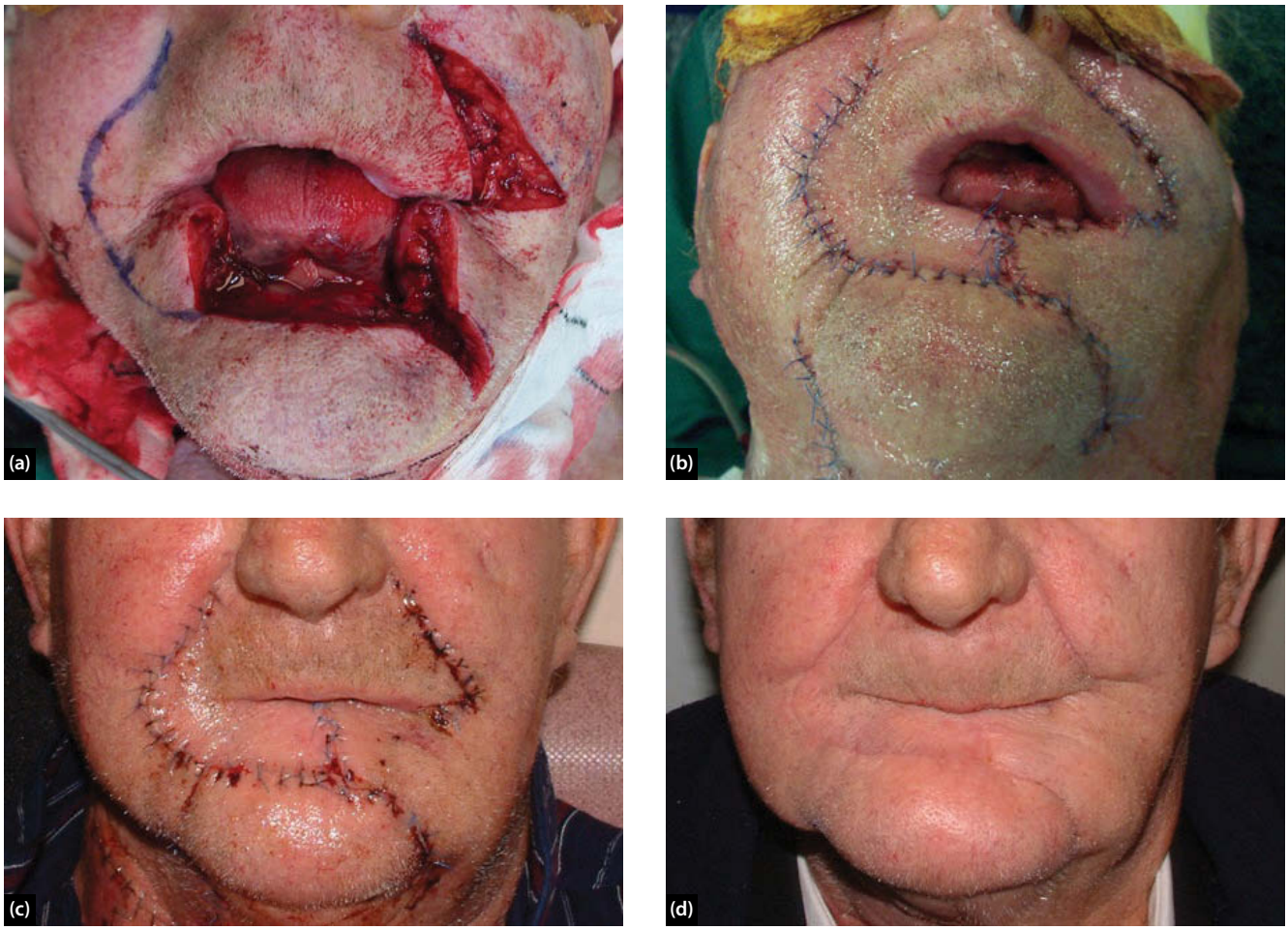


Figure 12.22 **(a)** Subtotal defect of the lower lip, with left cheek advancement performed and right Karapandzic flap designed. **(b)** Intra-operative appearance. **(c)** Immediate post-operative appearance. **(d)** Appearance at 3 months.

excisions, in contrast to the full-thickness tissue excision of the older procedure.

Bilateral cheek advancements can be used for total lower lip reconstruction, but there can be significant facial scarring. For the best function, it is important to reconstruct the orbicularis muscle. An alternative for total or subtotal lip reconstruction is to combine unilateral cheek advancement with a contralateral Karapandzic flap (**Figure 12.22**).

The 'bandoneon' technique[241]

A bandoneon is a type of concertina, which is particularly popular in Argentina as an accompaniment to Tango. A mucomusculocutaneous flap from the lower lip can be stretched like a 'bandoneon' and advanced to reconstruct lower lip defects up to two-thirds in width. A zigzag incision through skin, muscle and mucosa is made laterally from the lip defect as far as, or just beyond, the contralateral oral commissure. The incision is placed at the junction of lip and chin. The lower lip flap is then completely freed and stretched towards the lateral border of the lip defect and sutured in three layers (**Figure 12.23**). The zigzag incision facilitates this stretching, akin to the stretching of a bandoneon. In central defects, bilateral flaps can be raised.

Because the orbicularis oris is preserved in the flap, functional outcomes of this reconstruction are good. The oral commissure is shifted medially, however, and microstomia can result from large reconstructions.

The steeple flap[242]

This is an island flap of full-thickness tissue from the cheek. The lower lip defect is first converted to a rectangle. The lower line of excision is then extended laterally for a distance equal to the height of the resectional defect. Two vertical lines are drawn cranially from this line for a distance equal to the length of the lip defect. Thus, a rectangular island flap is marked out to the same dimensions as the rectangular lip defect. A triangle is marked on top of the proposed island flap – this will allow straight-line closure of the wound. The facial artery and its branches are marked with the aid of a hand-held Doppler probe. The flap is then incised full-thickness on its superior, medial and inferior margins. On the lateral margin, the facial artery and a small cuff of soft tissue are preserved. Depending upon the site of entry of the facial artery into the flap, the flap is transposed into the lip defect with either its lateral or medial border forming the upper border of the reconstructed lip. An excess of mucosa is cut

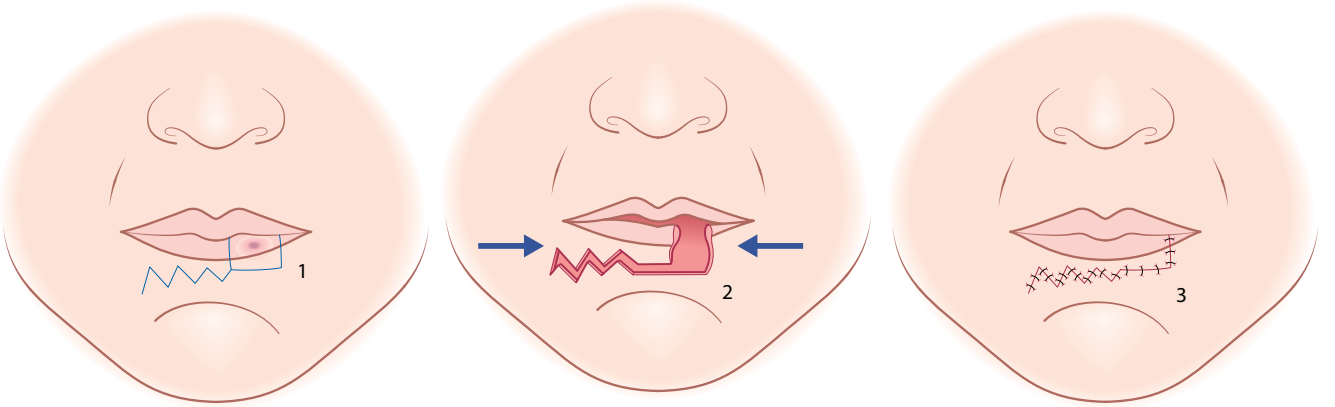


Figure 12.23 Bandoneon flap. 1. Mark out the excision margin and from the lower border of the excision extend a multiple w-plasty just past the commissure following the labiomental junction. 2. Full thickness excision of the lesion and full thickness incision along the lateral zig-zag markings through skin, muscle and mucosa. 3. Advance the lower lip to close the defect.

with the flap; this is used for vermilion reconstruction. For total lower lip reconstruction, bilateral steeple flaps can be used.

This technique avoids significant microstomia, but motor and sensory recovery may be delayed or incomplete.

Microsurgical reconstruction[238]

Subtotal and total reconstruction of the lower lip can be performed by free-tissue transfer, especially when there is scarring or inadequate laxity of the cheeks. Such reconstructions are never natural looking and have poor functional results and should only be used as a last resort. A folded free flap, such as the radial forearm flap, is the best option. The height of the reconstructed lip can be maintained by using the palmaris longus tendon to suspend the flap. This helps with oral continence. Should a sensate reconstruction be required, the lateral antebrachial cutaneous nerve can be anastomosed to the mental nerve.

KEY POINTS

- Lip tissue is precious and should never be discarded unnecessarily.
- Remaining lip tissue is the best option for reconstruction of small to medium lip defects.
- When a lip defect is too large to be reconstructed with remaining lip tissue, adjacent tissue such as the cheeks should be used.
- Reconstruction by distant tissues, such as free-tissue transfer should only be performed when there is insufficient local tissue to reconstruct the defect.

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CHAPTER 13

OROPHARYNGEAL TUMOURS

Terry M. Jones and Mererid Evans

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SEARCH STRATEGY

The data in this chapter are based on a search using the following keywords: head and neck cancer, oropharynx cancer, human papillomavirus, transoral laser surgery, transoral robotic surgery, intensity-modulated radiotherapy (IMRT) and clinical trials.

INTRODUCTION

The rapid increase in the incidence of Human papillomavirus – associated oropharyngeal carcinoma (HPV+OPSCC) seen in many countries of the developed world over the last several decades has resulted in a major healthcare problem which requires a major reassessment of the way oropharyngeal carcinoma is diagnosed and treated.

This discrete and novel disease entity presents in younger, fitter, more affluent patients who drink less alcohol and smoke less tobacco compared with patients who present with HPV negative (HPV-) squamous cell carcinoma of the head and neck. Paradoxically, their tumours, which typically present with clinicopathological features (multiple cervical lymph nodes with a high prevalence of extracapsular spread) traditionally considered as harbingers of poor outcome, respond more favourably to treatment.

Whilst this is to be welcomed, contemporary treatments result in high levels of early and long-term toxicity, particularly impacting negatively on swallowing function. As a consequence, greater numbers of younger patients, whilst being cured of their disease, are left with poor swallowing function which has a major impact on health-related quality of life.

Although most patients with HPV+OPSCC do well, a subgroup of patients, who are currently undetectable prior to treatment, together with patients with HPV-OPSCC, still do poorly. This dichotomy in presentation and outcome has resulted in a clinical conundrum for those clinicians treating patients with OPSCC. Whilst, on the one hand there is an urgent need to find novel de-intensified treatments which maintain the advantageous survival outcomes but confer better swallowing outcomes for patients with HPV+OPSCC, there is also a need to define treatments which will improve survival for patients with HPV-OPSCC.

This quest for novel treatments, as well as renewed interest and use of transoral surgical approaches, has re-opened the debate regarding the role of surgery in OPSCC.

Moreover, a better understanding of the biology of HPV+OPSCC is essential if truly novel treatments and accurate methods of risk-stratification are to be developed – particularly in this exciting era of emerging immunotherapeutic interventions.

Prior to any attempt to de-intensify treatment or to accurately prognosticate, there is a need to develop assays with high specificity to ensure HPV status is accurately determined. This necessity has resulted in significant research efforts over recent years to define the most appropriate assays and testing algorithms.

As well as simply trying to understand the emergence of HPV+OPSCC, the advent of prophylactic vaccination and its role in the prevention of HPV+OPSCC has resulted in an urgent need to understand the epidemiology

of HPV+OPSCC better and, in particular, to define better the apparent wide geographical variation seen between and within countries.

Furthermore, in order to address the void of high-quality data relating to the management of HPV+OPSCC, several groups around the world have developed exciting clinical trials, the results of which are awaited with interest.

These issues, which will be discussed in greater detail in the following chapter, conspire to make it a fascinating and potentially rewarding time to be involved in the treatment of patients with HPV+OPSCC.

SURGICAL ANATOMY OF THE OROPHARYNX

The pharynx is a fibromuscular tube forming the upper part of the respiratory and digestive tracts. It extends from the base of the skull to the level of the sixth cervical vertebra at the lower border of the cricoid cartilage where it becomes continuous with the oesophagus. It is divided into three parts: the nasopharynx, oropharynx and hypopharynx. The oropharynx is bounded superiorly by the soft palate, inferiorly by the upper surface of the epiglottis (the lingual surface of the epiglottis to the tip is included in the oropharynx), anteriorly by the palatoglossal arches and the vallate papillae of the tongue and laterally by the pharyngoepiglottic folds. It follows that the posterior third of the tongue, including the vallecula, is included in the oropharynx as are the palatine tonsils situated in the lateral walls between the palatoglossal arches anteriorly and the palatopharyngeal arches posteriorly (previously called the anterior and posterior faucial pillars). The lateral wall, and therefore the tonsil, takes most of its blood supply from the facial artery. Laterally, there is a rich plexus of paratonsillar veins, which may be the source of serious venous bleeding during surgery. The section of posterior pharyngeal wall included in the oropharynx lies anterior to the vertebral bodies of C2 and C3 and extends from a horizontal line drawn through the hard palate cranially to a horizontal line drawn through the hyoid bone caudally.

The oropharyngeal wall comprises four layers. The inner mucosal lining is surrounded by the submucosa. Outside the submucosa is the muscular layer made up of the superior and inferior constrictor muscles, together with the stylopharyngeus, paltopharyngeus and salpingopharyngeus muscles. These, in turn, are surrounded by the outermost buccopharyngeal fascia layer which is separated posteriorly from the prevertebral fascia by the potential retropharyngeal space which is functionally important, allowing free movement of the pharynx on the vertebral column during swallowing, respiration, speech and exercise. The space itself, and the retropharyngeal lymph nodes contained within it, are also of importance in disease when considering the spread of oropharyngeal infection and malignancy.

Surgical access to the structures of the oropharynx may be achieved transorally, anteriorly via mandibulotomy or inferiorly and laterally from the neck. The route chosen will be determined by the anatomical site and/or nature of the pathology as well as the surgical aim.

Microscopic anatomy

The oropharynx, like the remainder of the pharynx, is predominantly lined with stratified squamous epithelium which is predominantly non-keratinizing although islands of keratinizing epithelium may be seen and become more numerous with age, presumably as a consequence of repeated mucosal trauma / irritation. Interspersed through the mucosa are numerous mucous secreting cells as well as minor salivary glands which are most concentrated on the oral surface of the soft palate.

The oropharynx also contains an abundance of lymphoid tissue, in particular the palatine and lingual tonsils which form the anterolateral components of Waldeyer's ring. It is important to appreciate that these aggregates of lymphoid tissue are covered by pharyngeal mucosa which, particularly in the case of the palatine tonsil, form epithelial crypts which extend deep towards the centre of the tonsils. A particularly large crypt is seen at the boundary of the caudal 2/3 and cranial 1/3 of the tonsil. This intratonsillar cleft is the remnant of the embryonic second pharyngeal cleft.

An appreciation of the histology of the structures of the oropharynx is important when considering the histiogenesis of the various tumours which may arise.

FUNCTIONS OF THE OROPHARYNX

The oropharynx is involved in three primary functions, namely swallowing, speech production (articulation) and host defence against ingested or inspired pathogens.

The movements of the muscular wall, base of tongue (BOT) and soft palate are critical in the former two activities, described in greater detail in Chapters 48, Physiology of swallowing and 60, Voice and speech production, whilst the lymphoid tissue of Waldeyer's ring is the primary effector of the latter.

TUMOURS OF THE OROPHARYNX

Benign

Whilst benign tumours may originate from any of the structures of the oropharynx, apart from mucous retention cysts of the vallecula and tonsil, they are extremely rare. Papillomas are the most common benign tumour and are often found incidentally on routine examinations of the throat.

In almost all instances where intervention is decided upon, surgery is the treatment of choice, the nature of which is dictated by the size, position and histology of the tumour.

Deep lobe parotid tumours, most commonly pleomorphic salivary adenomas, whilst not strictly tumours of the oropharynx, may present as an asymmetric mass protruding into the pharynx and/ or soft palate. Surgical excision as part of a partial or total parotidectomy procedure is usually recommended. In most cases, complete excision is achieved by a solely lateral approach as for a total parotidectomy although, on occasion, a combined approach, involving a lip-split mandibulotomy for access, may be necessary for larger or less accessible tumours.

Malignant

LYMPHOMA

Lymphomas arising in the oropharynx, whilst rare, are not uncommonly seen by otolaryngologist – head and neck surgeons. They are almost exclusively non-Hodgkin lymphomas and arise in the lymphoid tissue of the palatine tonsil or BOT. They particularly present in younger patients (45–55 years) and whilst diagnosed by biopsy, are thereafter treated by haemato-oncologists and accordingly their management is beyond the scope of this chapter.

MINOR SALIVARY GLAND TUMOURS

Salivary gland cancers account for up to 6% of all head and neck malignancies and therefore are rare. Approximately 20% of all salivary gland cancers arise in the minor salivary glands (MiSG) and in contrast to the parotid most (80%) tumours of the MSG are malignant. The hard and soft palate are the commonest sites for MSG cancers.

The World Health Organisation lists 24 different malignant histological subtypes, the four most common of which are mucoepidermoid carcinoma, adenoid cystic carcinoma, adenocarcinoma and salivary duct carcinoma.[1]

Surgical resection with adequate surgical margins is the primary treatment of choice. The surgical approach used for MSGs of the oropharynx will depend on the site and size of the mass and the likely functional deficit following resection, and may range from a transoral resection to a major open resection with microvascular free-flap reconstruction. Post-operative radiotherapy is often used, particularly in patients with high-risk factors, although the radiosenstivity of MSG cancers is highly variable. There is no evidence for the use of post-operative chemoradiotherapy Chemoradiotherapy (CRT) and elective treatment of the N0 neck is controversial. A recent systematic review, whilst accepting the lack of availability of good quality data, recommended the following:[2]

- Complete surgical resection should remain as the mainstay treatment.
- A therapeutic neck dissection should be used to treat patients with clinical or radiological evidence of cervical lymph node metastasis.
- An elective neck dissection for patients with no evidence of cervical lymph node metastasis should probably be reserved for patients with advanced stage or high-grade tumours, particularly for mucoepidermoid carcinoma and adenocarcinoma.
- Post-operative radiotherapy (RT) should be recommended for patients with adverse prognostic features such as T3 or T4 tumours, close or involved resection margins, high-grade, perineural or perivascular invasion and N+ disease.
- The use of PORT for T1-weighted and T2-weighted tumours in the absence of adverse prognostic features is not supported.
- For patients with inoperable disease, or who refuse surgery, primary RT should be considered.
- The value of targeted therapies for advanced and/or metastatic disease has yet to be confirmed.

OROPHARYNGEAL SQUAMOUS CELL CARCINOMA

Epidemiology

Squamous cell carcinoma (SCC) is the commonest malignancy presenting in the oropharynx. Over recent decades, across the developed world, there has been a substantial increase in the incidence of oropharyngeal squamous cell carcinoma (OPSCC) affecting the tonsils, tongue base and soft palate. The incidence of OPSCC in the UK underwent a 2-fold increase between 2002 and 2011 [age-standardized rate 2002: 2.1 (95% confidence interval (CI), 1.9–2.2); 2011: 4.1 (95% CI, 4.0–4.3)].[3] (**Figure 13.1**) Whilst alcohol and tobacco use have been well documented as individual or synergistic risk factors for the development of SCC of the head and neck,[4] over the last three decades accumulating evidence has confirmed

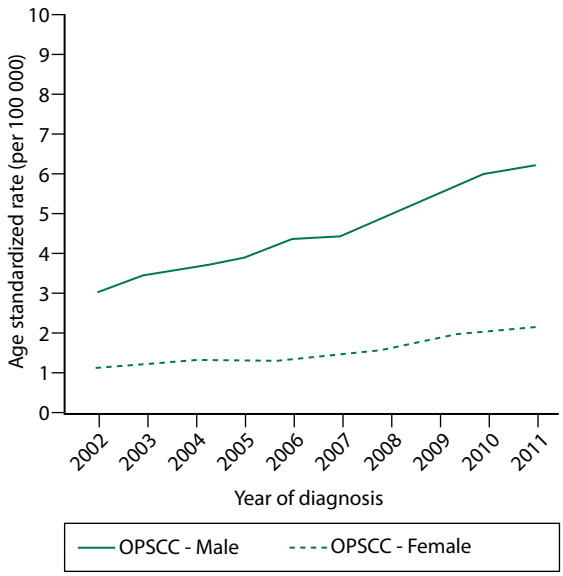

Figure 13.1 Age standardized rate of OPSCC in the UK, 2002–2011. Reprinted from Schache et al, *Cancer Res*; 2016 by kind permission AACR publications.[3]

that human papilloma virus (HPV) – specifically genotype 16 – is an additional, independent, risk factor for OPSCC.[5]

In a recent UK multicentre, cross-sectional study the HPV status of archival tumour tissue blocks collected from 1602 patients diagnosed with OPSCC between 2002 and 2011 was determined. The overall proportion of HPV-positive OPSCC was 51.8% [95% CI, 49.3–54.4] and this remained unchanged throughout the decade [unadjusted RR = 1.00 (95% CI, 0.99–1.02)]. In view of the doubling in incidence, it was concluded that the absolute number of both HPV-positive and HPV-negative cases in the UK was increasing (**Figure 13.2**).[3]

These UK data contrast with published data from other parts of the world where substantial variation has been reported in the proportion of OPSCC attributable to HPV between countries and time periods. This is likely to be a reflection of variations in multiple factors, which may include sexual behaviour and rates of genital HPV infection, as well as tobacco and alcohol consumption and highlights that trends in the aetiology of OPSCC must be considered in a population-specific manner.

Non-HPV associated OPSCC

HPV-OPSCC shares the same risk factors as other SCCs of the head and neck and the pathogenesis of malignant transformation is thought to be similar. Detailed consideration of the pathogenesis of non-HPV-associated OPSCC is therefore, provided in Chapter 6, Introducing molecular biology of head and neck cancer.

In contrast, HPV-associated transformation is limited to the oropharynx and is therefore considered in greater detail below.

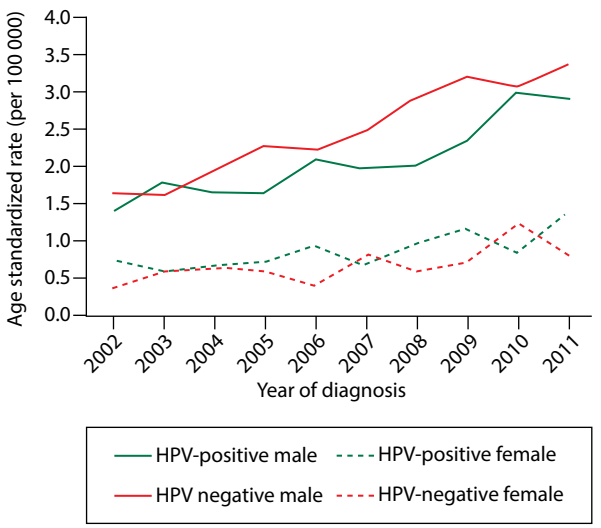

Figure 13.2 Estimated age standardized incidence of HPV-positive and HPV-negative OPSCC in the UK, 2002–2011. Reprinted from Schache et al, *Cancer Res.* 2016 by kind permission AACR publications.[3]

HPV-associated OPSCC

ORAL HPV INFECTION

Prevalence rates

An obvious risk factor for the development of HPV-associated OPSCC (HPV+OPSCC) is an oral infection with high-risk HPV (HRHPV). It follows therefore that an understanding of the epidemiology of HPV oral infection is important when trying to understand the development of HPV+OPSCC and this is comprehensively reviewed in Chung et al.[8]

Data from the US suggest that the prevalence of oral HPV infection is much lower than the prevalence of genital HPV infection: epidemiological studies involving a variety of US populations confirmed a genital infection rate ranging from 27% to 43% in females aged 14–59 years, compared with an oral HPV infection rate ranging from 0.9% to 7.5% in 13–30 year-old men and women.[9–14]

Systematic review data[15] which included 18 studies published between 1997 and 2009 involving ~4500 healthy individuals concluded that the rate of oral infection with any HPV genotype was 4.5% in comparison with 3.5% for infection with any HRHPV genotype and 1.3% for infection with HPV-16.

Similar rates were confirmed in a landmark National Health and Nutrition Examination Survey (NHANES) published in 2012.[9] This cross-sectional study, conducted in 2009–10, involved a general US population comprising ~5500 US men and women. All participants provided mouthwash samples from which DNA was extracted and tested for the presence of one or more of 37 HPV genotypes. Overall prevalence of HPV infection was 6.9%, whilst infection with HRHPV was 3.9% and infection with HPV-16 was 1%.

Whilst similar to the data obtained from the systematic review highlighted above, the overall prevalence identified in the NHANES study was higher, perhaps reflecting the fact that the NHANES data were collected some years later than much of the data included in the systematic review.

Whilst the 'snap-shot' infection rate with HPV-16, at 1%, is low, it is important to reflect that this amounts to >2 million US citizens with an oral HPV infection at any given point in time.

Interestingly, in common with anal and penile HPV infection rates, the prevalence of oral HPV infection has a bimodal distribution with respect to age. The first and smaller peak (~7%) is seen in patients in their early 30s whilst a second peak (~11%) is seen in patients, particularly men, in their early 60s.

Risk factors

Sexual activity appears to be a prerequisite of oral HPV infection as studies have shown that HPV infection coincides with sexual debut. There is also some evidence that vertical transmission, from infected birthing mother to child, is possible resulting in neonatal oral HPV infection.

Whilst an increased number of oral sexual partners have been demonstrated in most studies to correlate with oral HPV prevalence, some studies do not support this assertion.

The NHANES study confirmed that oral HPV infection is increased 8-fold in sexually active individuals compared with individuals who had never had sex (7.5% vs 0.9%). The data also showed that the prevalence of oral HPV infection increased with the number of lifetime sexual partners (vaginal or oral) and with recent sexual activity, with the highest prevalence (>20%) seen in patients reporting >20 lifetime sexual partners.

However, as sexual practices are co-linear, it is difficult to ascertain with precision which sexual practice may result in transmission in any given situation. This is perhaps reflected in the data published by Kreimer et al,[16] which confirmed, in a multi-national study of healthy men, that men who reported never performing oral sex had a similar rate of oral HPV infection to those who reported performing oral sex (3.8% vs 4.1%).

It has been hypothesized that auto-inoculation (oral infection transmitted from infected genitalia in the same individual) may be a significant route of oral HPV infection. There is however, scant evidence to support this. As well as the wide discrepancy between genital and oral infection rates in the same individual, meta-analysis data confirm only a 27% HPV type-specific concordance between genital and oral infection in dually infected women.[17]

It is also clear that additional risk factors are important in the development of oral HPV infection. The NHANES study confirmed that male gender and tobacco use were also important risk factors, as 10% of men were infected in comparison with 3% of women and individuals smoking >21 cigarettes per day had a 20-fold increased risk of oral HPV infection compared with non-smokers. Kreimer et al[16] also established that current tobacco use resulted in a doubling of the odds of an oral HPV infection.

Natural history

As with the epidemiology of oral HPV infection, detailed knowledge of the natural history is also lacking. Existing data suggest that the vast majority of oral HPV infections are cleared within 1 year of infection. For example, Kreimer et al,[18] showed that 85% of incident infections were cleared within 1 year which is similar to the data reported by Moscicki et al,[19] for cervical cancer where they reported that only 10% of women had persistent infection 2.5 years after initial detection.

Link between oral HPV infection and OPSCC

As might be expected, oral HPV infection and other common risk factors have been shown to be associated with the development of OPSCC. For example, HPV-16 DNA is found in ~50% of oral rinses provided by patients with diagnosed OPSCC[20] and patients with OPSCC are 12 times more likely than patients without OPSCC to have an oral HPV infection, a risk which increases 15-fold when HPV-16 infection alone is considered.[21] Moreover, patients with HPV+OPSCC report an increased number of sexual partners.[9]

As well as being a risk factor for oral HPV infection, tobacco use is also associated with an increased risk of HPV+OPSCC.[22, 23] Although median tobacco use is less for patients with HPV+OPSCC compared with those patients with HPV-OPSCC, the majority of patients presenting with HPV+OPSCC are still current or past smokers.[22, 24]

What is clear from increasing numbers of studies is that tobacco use is a dose-dependent risk-stratifier of outcome for patients with HPV+OPSCC, accepting the fact that tobacco use is a likely surrogate of underlying tumour genome mutation load and genetic instability.[6, 7]

Molecular biology of human papillomavirus infection

Virology

The link between HPV and OPSCC was first postulated as early as 1983 by Syrjanen et al[25] A subsequent and increasing volume of clinical data have confirmed its association and HPV-16 is now considered a causative agent.[5]

HPV is a member of the family of papillomaviridae, a virus family recognized in 2004 by the International Council on Taxonomy of Viruses.[26]

The papillomaviridae, together with polyomaviruses, are non-enveloped and contain a circular double-stranded DNA genome. Instead of a phospholipid bilayer envelope derived from the host membrane on infection, they comprise icosahedral capsids in the absence of an envelope.[27] They are obligate epitheliotropic human pathogens in that they have a predilection for infecting human epithelium.

The double-stranded DNA (dsDNA) HPV genome is approximately 8 Kb long and contains eight genes, six of which are expressed early in an infection (*E1, 2 & 4–7*) whilst two are transcribed later in the viral infection cycle (*Ll & 2*). *E1* and *E2* are regulatory genes, controlling the transcription of the remaining genes.[28] Of particular note, *E5–7* are involved in host-cell transformation, and are therefore potentially oncogenic, *L1* and *L2* are structural proteins necessary for the formation of the viral capsids.[29]

Currently, over 200 different genotypes of HPV have been identified. More than 150 have had their genomes completely sequenced and of these 12 have been designated 'high-risk' due to their propensity to provoke malignant transformation of the epithelial cells they have infected.[30] Of these, HPV-16 and -18 are the most important, causing ~70% of HPV-related cancers of which, in addition to oropharynx, the most common are cervix, vagina, vulva, anal and penile.

In OPSCC there is a greater dominance of the HPV-16 genotype compared to cervical cancer (~95% vs ~60%). Why this might be unclear, it may reflect the fact that the different mucosal environments may support the infection of specific genotypes. Conversely, it may reflect a difference in local genotype-specific mucosal immune response.[31]

HPV induced transformation

Little is known about the mode of transmission, route of infection or life cycle of HPV in the epithelium of the oropharynx. Accordingly, much reliance is placed on data derived from cervical cancer research for our current understanding of HPV infection, life cycle and oncogenesis.

Whilst extrapolation of this knowledge to the situation in the oropharynx is necessary as alternative data currently do not exist, this should be done with caution as although there are many similarities in the mucosal structure of both anatomical sites, there are also many differences.

In the transformation zone, between columnar and stratified squamous epithelium in the cervix, the squamous epithelium is stratified, organized in layers of increasing cellular differentiation from deep to superficial. The specific epithelial layers are the basal, para-basal, stratum spinosum and the most superficial desquamating strata.

The basal layer is in contact with the basement membrane and has a low turnover rate. In contrast, the para-basal layer has a high mitotic rate and therefore a rapid turnover of cells.

In the cervix it has been established that microabrasions of the surface epithelium facilitate virus particle infection of the basal and para-basal layer of cells (**Figure 13.3**).[32]

Following infection, the dsDNA viral genome remains in its circular, episomal form in the cytoplasm of the host cell. The virus harnesses the transcriptional and translational machinery of the host cell to instigate viral gene expression followed by viral replication, thereby completing its life cycle.

Transient infections are the norm in the cervix, however, a minority of individuals are unable to clear the initial infection resulting in a chronic inflammatory state. It is assumed that an even smaller percentage of these individuals then progress to develop cervical intraepithelial neoplasia (CIN) prior to developing invasive malignancy. It is important to note that no premalignant lesion similar to CIN has ever been detected in the oropharynx.

For the majority of the cases (85%) proceeding to malignant transformation, viral integration into the host genome is a critical step which results in disruption of the transcriptional repressor gene (*E2*) with the subsequent unregulated expression of the viral oncogenes *E6* and *E7*.[33] The mechanisms by which the remaining 15% of cases in which the dsDNA genome remains in its episomal form, yet still mediates malignant transformation,

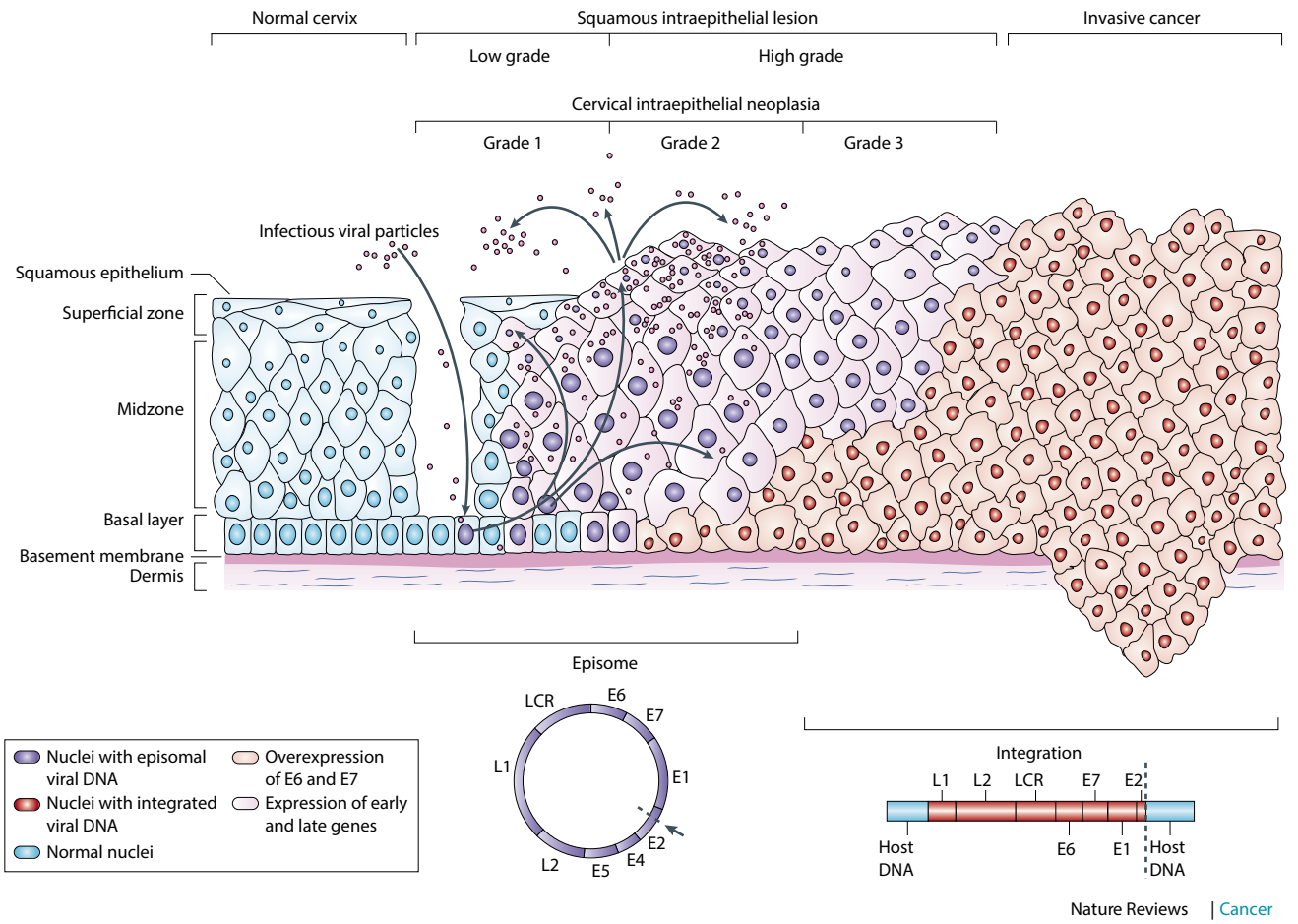

Figure 13.3 A schematic representation of (1) HPV virus infection of the basal layer of cervix mucosa as a consequence of the development of microabrasions. (2) The natural history of the virus life cycle, with virion production which is dependent upon and coincident with the differentiation of the mucosal epithelium prior to release as consequence on epithelial desquamation at the mucosal surface. **(3)** In contrast, the integration of viral genome into host genome resulting in basal cell immortality and cellular progression through dysplasia to invasive neoplasia. Reprinted Woodman CBJ, et al. The natural history of cervical HPV infection: unresolved issues. *Nat Rev Cancer* 2007; **7**: 11–22.

is the subject of ongoing research.[34] A simple model of integration defining the start of a transition to malignancy seems less likely when consideration is made of the relatively low (21–43%) viral integration rates seen in OPSCC.[35] However, epigenetic regulation of the viral Long Promoter Region, from which *E2* transcription is regulated, has been implicated.[36]

The genomes of all eukaryotic organisms are under tight transcriptional control.[37] Whilst certain genes act to switch other genes on to potentiate cell growth and division, antagonistic pathways exist to ensure the regulation of cell growth and division. In order for a cell to grow and divide it needs to advance through the cell cycle. There are four main periods of the cell cycle. G1 is a period of quiescence before the onset of S phase DNA replication. Following completion of DNA replication, S phase is followed by another gap phase, G2, in which cells prepare themselves for mitotic division during M phase. The eukaryotic cell cycle is tightly regulated and various molecular checkpoints exist throughout the cell cycle. At each checkpoint competing growth promoting and growth inhibiting signals are assimilated by the cellular molecular machinery and a 'decision' for the cell to proceed to the next stage of the cell cycle or for progression to become impeded is made. Tumour suppressor protein (TSP) expression is critical for the coordinated progression of the cell through each cell cycle checkpoint. Any perturbation of this checkpoint control mechanism will result in disordered cell cycling and aberrant cell growth, including the ultimate development of cancer.

Two of the most well understood TSPs are p53 and the retinoblastoma protein (pRb). p53 has been called the 'guardian of the genome' in light of its many varied roles in ensuring that cell growth and division does not continue unchecked as a consequence of DNA damage. Broadly, when a given cell is exposed to cellular stress and/or DNA damage, p53 is able to mediate cell cycle arrest followed by either DNA repair or programmed cell death if DNA repair proves impossible.

In contrast, pRb exerts its influence in late G1. If pRb is not phosphorylated it binds to and suppresses the E2F family of transcriptional activators. However, if pRb is phosphorylated it releases its inhibitory grip on the E2Fs allowing them to invoke the transcription of downstream genes whose actions are necessary for the cell to progress from G1 to S phase. Thus pRb is essential in preventing unregulated progression of cells from G1 to S. A notable product of downstream gene transcription is the expression of $p16^{INK4a}$ a protein, as will be seen below, whose expression is utilized to infer 'active' HPV infection.

It is via interactions with p53 and pRb that HPV exerts its primary oncogenic effects. Amongst other mechanisms, *E6* is able to bind p53 whilst *E7* binds pRb. In both cases this results in the degradation of both TSPs by the proteosome. Any cell losing the actions of these two key TSPs is well on the way to becoming a cancer. The effects of their loss will be subsequently augmented by a trend towards genetic instability and ultimately tumourigenesis promoted by the loss of their regulatory pathways (**Figure 13.4**).

HPV detection in clinical practice

HISTOPATHOLOGY

It has been well established that HPV+OPSCC presents with characteristic histopathological features. In contrast to HPV-SCCs which are typically moderately differentiated and keratinizing tumours arising from dysplastic epithelium, HPV-associated tumours are non-keratinizing, display a poorly differentiated predominantly basaloid morphology, are not associated with surface dysplasia but are associated with a high level of tumour infiltrating lymphocytes (TILs), the density of which have been shown to have prognostic value (**Figure 13.5**).[38] Although characteristic, these features are not diagnostic and a combination of molecular testing is required to establish a diagnosis of HPV-associated OPSCC in the oropharynx. Issues relating to the diagnosis of HPV+OPSCC is comprehensively reviewed in Robinson et al.[39]

MOLECULAR TESTING FOR HPV STATUS

It is insufficient to simply detect the presence of HPV DNA within a given tumour cell as a positive result may simply reflect a previous or bystander infection which resulted in inconsequential viral genome integration into the host genome or potential contamination with HPV DNA. Therefore, a necessary requirement for HPV testing is, in addition to demonstrating the presence of HPV DNA, to demonstrate some evidence of downstream HPV-driven biological activity. This is a particularly important issue when de-intensification of treatment – typically in the context of clinical trials (see later section) – is considered for patients with HPV+OPSCC.

TESTS FOR HPV DNA

Two types of diagnostic strategy are commonly used to detect the presence of HPV DNA within tumour cells.

In-situ hybridization (ISH)

This method relies on the use of a DNA probe labelled, for example, with a chromogen, the nucleotide sequence of which is complementary to the DNA sequence or gene under investigation. When applied to formalin-fixed paraffin embedded (FFPE) tumour samples, the probe will bind to the complementary sequence within the DNA of that tissue sample, thereby confirming its presence. The chromogen label allows the visualization of the bound probe by light microscopy. Kits are commercially available for the detection of HRHPV genotypes in FFPE tissue and are typically designed to detect the specific *L1* gene sequences, variations of which determine the specific genotype. A positive test result is confirmed by the presence of a blue dot under light microscopy (**Figure 13.6**). This technique allows localization of the HPV DNA to the host cell nucleus and whilst a punctate staining pattern is suggestive of HPV DNA integration it does not amount to categorical proof of this.

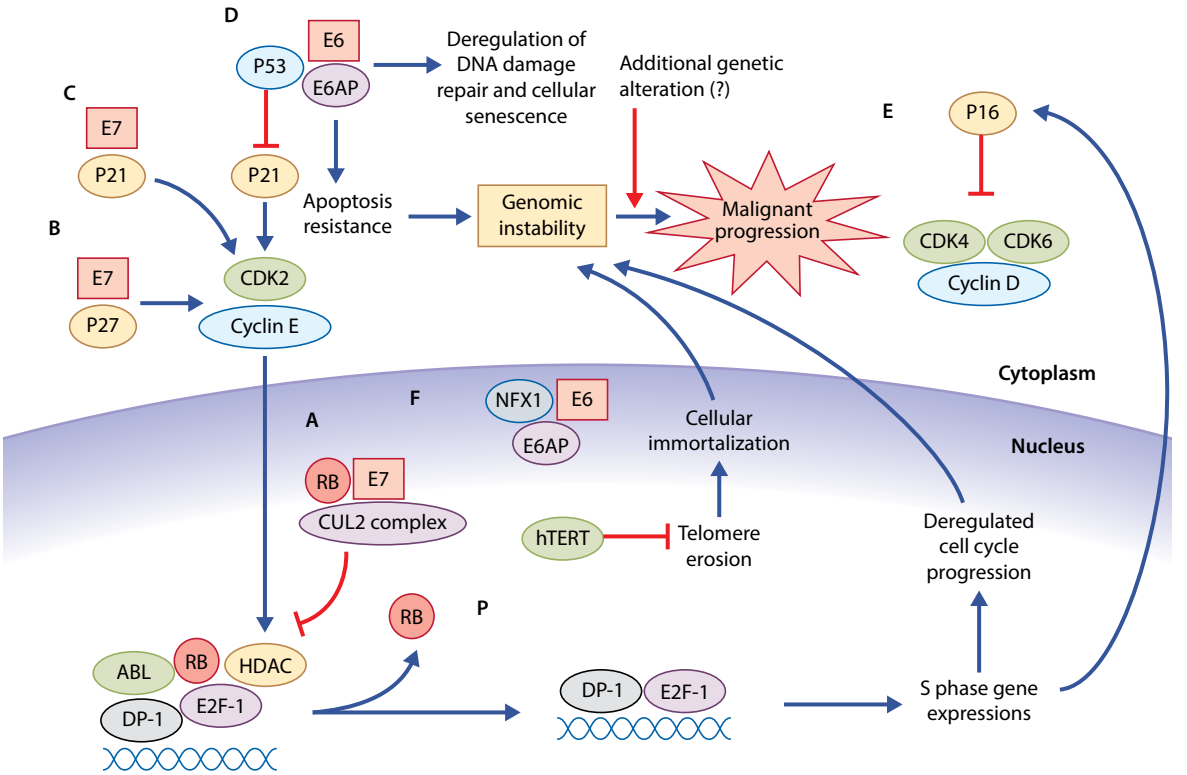

Figure 13.4 A schematic representation of the molecular pathways contributing to E6 and E7 mediated malignant transformation of normal keratinocytes. (A) Proteasomal degradation of retinoblastoma tumour suppressor protein (RB) as a consequence of binding by HPV oncoprotein E7 in association with the cullin 2 ubiquitin ligase complex. (B) Interaction between E7 and p27 resulting in inhibition of cell-cycle arrest. (C) Interaction between E7 and p21 resulting in inhibition of cell-cycle arrest. (D) Proteasomal degradation of p53 TSP as a consequence of binding by HPV oncoprotein E6 in association with the ubiquitin ligase E6AP. (E) Increased expression of $p16^{INK4A}$ as a result of loss of E2F repression which in turn results from RB degradation. (F) E6 and E6AP degradation of NFX1 resulting in the loss of repression of hTERT and a consequent reduction in telomere erosion thereby contributing to the development of cellular immortality. (Source adapted from Chung, CH & Gillison, ML.)[29]

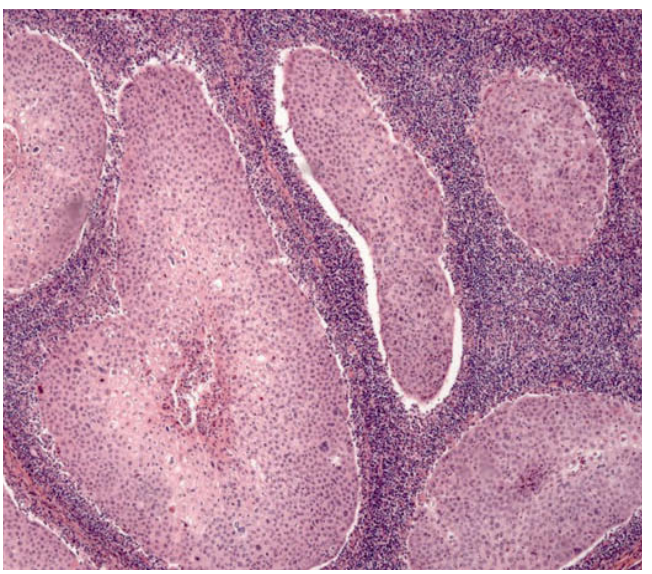

Figure 13.5 Image shows an H&E stained section of an oropharyngeal SCC. Tumour islands are surrounded by a dense infiltrate of lymphocytes. Magnification x50. By kind permission, Professor Gareth Thomas, University of Southampton.

Polymerase chain reaction (PCR)

This is a standard laboratory technique used to amplify short sequences of DNA. It is a highly sensitive technique which is able to augment a single copy of a given DNA sequence. Following the separation of double-strand DNA (dsDNA) into single-strand DNA (ssDNA), the presence of HPV DNA is detected using small targeted DNA sequences (primers) which are designed to bind to complementary DNA sequences on either side of the DNA segment (gene) under investigation: It is common to attempt to detect the presence of the HPV *E6* gene. Repeated cycles of the PCR will exponentially augment single copies of the specific gene under investigation allowing its detection with ease. This technique can be used on FFPE tissue although the best results are achieved using fresh tissue. Consensus PCR simply detects the presence of HPV DNA whilst real-time PCR is able to quantify viral load.

TESTS TO DETERMINE BIOLOGICAL ACTIVITY

Again two strategies are commonly used.

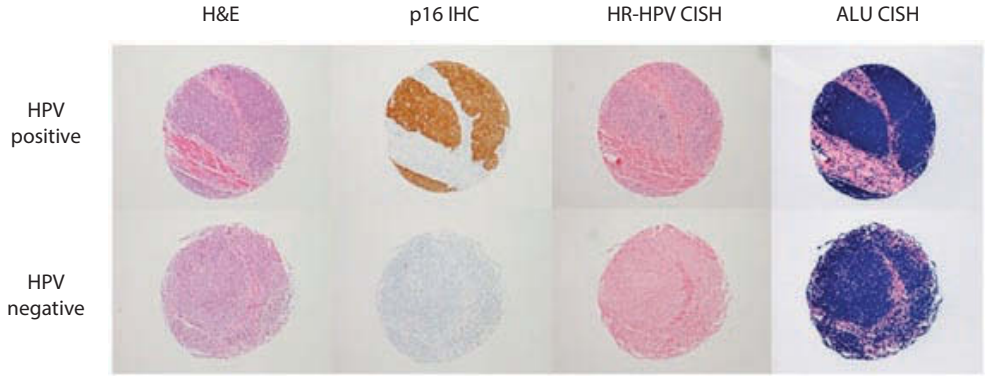

Figure 13.6 Panel of routine diagnostic tests applied for HPV status determination in OPSCC in the UK. **Columns from left**; Haematoxylin & Eosin (H&E), p16 immunohistochemistry (IHC), High-risk HPV chromogenic in situ hybridization (HR-HPV CISH), positive control (ALU CISH). **Top row** HPV positive OPSCC (p16 positive, high-risk HPV positive). **Bottom row** HPV negative OSPCC (p16 negative, high-risk HPV negative). (0.6 mm tumour cores). (By kind permission, Mr Andrew Schache, University of Liverpool).

Direct detection of E6 and E7 transcription

Quantitative Reverse Transcription – Polymerase Chain Reaction (qRT-PCR): Direct detection of E6 and E7 mRNA moves beyond merely detecting the presence of HPV DNA and aims to show HPV DNA is being transcribed resulting in the expression of E6 and E7 mRNA which have oncogenic properties and are presumed to be involved in tumorigenesis. The method most commonly used is quantitative reverse transcription PCR (qRT-PCR) by which complementary DNA (cDNA) is synthesized using the E6 or E7 mRNA transcript as a template. Thereafter, PCR, utilizing primers to the E6 and/or E7 cDNA sequence, is used to amplify the copy number of the cDNA transcripts. This technique is costly and labour intensive and has traditionally been restricted to frozen tissue. However, it constitutes the current gold standard assay for determining HPV biological activity.[24]

RNA-based Chromogenic In-situ-hybridization (RNA-ISH): This is a technique which also overcomes the dual testing requirements to firmly establish HPV status by detecting HPV specific E6/7 mRNA transcripts. This technique, which detects the presence of HPV E6 & E7 mRNA without the need for reverse transcription, is readily applied to the analysis of FFPE tissue. Therefore, in contrast to PCR techniques, it is potentially far easier to use in routine clinical practice. RNA-ISH performed on arrayed FFPE tissue cores has been shown to have a high level of sensitivity (97%) and specificity (93%) when compared with 'gold-standard' qRT-PCR performed on matched frozen tissue samples (**Figure 13.7**).[40] It is anticipated that RNA-ISH will become the routine standard for HPV testing in the foreseeable future. Commercial kits are readily available which contain probes for the E6 & 7 mRNA sequences of multiple HR HPV genotypes.

Surrogate markers

The surrogate marker most often used to detect HPV-induced transformation in the oropharynx is over-expression of $p16^{INK4a}$ using immunohistochemistry (**Figure 13.6**). It has been well established that the loss of $p16^{INK4a}$ is an early event in the development of tobacco and/or alcohol induced squamous cell carcinoma of the head and neck (SCCHN). However, by contrast, in HPV-associated SCCHN $p16^{INK4a}$ is typically intact. In non-transformed cells $p16^{INK4a}$ is negatively regulated by pRb. Consequently, when the effects of pRb are ameliorated by the actions of E7, $p16^{INK4a}$ levels are overexpressed.[41]

Immunohistochemistry to detect $p16^{INK4a}$ overexpression is easily performed on FFPE tissue samples. It is cheap, with well-established protocols and is widely available.

However, whilst its overexpression correlates well with clinical outcome[7] it is has low specificity for HPV infection as $p16^{INK4a}$ may also- be overexpressed by mechanisms other than the HPV-mediated inhibition of pRb in a minority (10–15%) of cases[24] for example Rb itself may be mutated.

Diagnostic algorithm

The Johns Hopkins Medical Institution diagnostic approach outlined by Westra[42] is one of the most widely accepted diagnostic algorithms in current use.

Using FFPE tissue, an initial screening of tumour tissue using IHC for $p16^{INK4a}$ is performed. Following this, all $p16^{INK4a}$ positive tumours undergo HPV-16 specific in-situ hybridization. All HPV-16+ / $p16^{INK4a}$+tumours are therefore designated as HPV-16+ve. The remaining minority of tumours which are $p16^{INK4a}$+/HPV-16 –ve then undergo further testing with an *in-situ* probe which is able to detect the presence of DNA of other HRHPV genotypes.

Such an algorithm is currently necessary in light of the variable sensitivity and specificity of the commonly employed individual tests and the need to demonstrate the presence of 'biologically active' HPV infection, and to ensure that tumours are correctly ascribed as being HPV+ve or not in the most cost effective and clinically convenient way.

CLINICAL PRESENTATION

Tumours which originate in the tonsil represent ~60% of all OPSCC tumours (**Figure 13.8**). In the context of HPV+OPSCC they are typically relatively small and

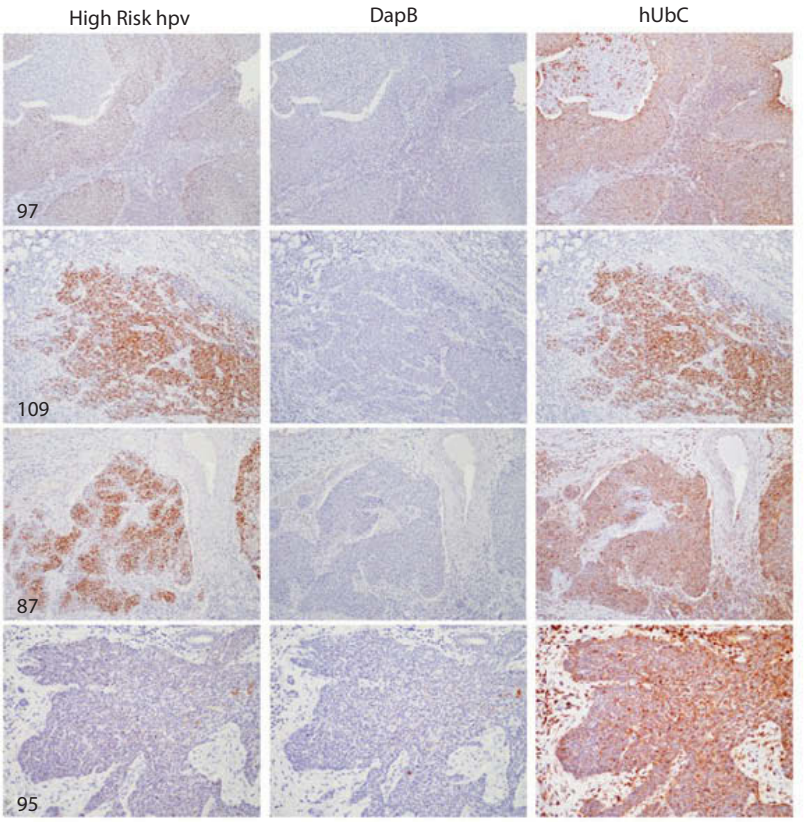

Figure 13.7 Photomicrographs of OPSCC stained using RNAscope with probes for high-risk HPV, dapB (negative control) and UBC (positive control). The cases demonstrate a range of positive staining patterns for high-risk HPV. Cases 109 and 97 showed strong and moderate staining, respectively, and contained HPV-16 E6/E7 mRNA by qRT–PCR. Case 87 showed strong staining and contained HPV-18 E6 mRNA by qRT–PCR. Case 95 showed weak staining and was negative for HPV-16 E6/E7 mRNA, HPV-18 E6 mRNA and HPV-33 E6 mRNA by qRT–PCR (false-positive result). Scale bars are equivalent to 200 mm for cases 109 and 87, and 50 mm for cases 97 and 95. (By kind permission, Mr Andrew Schache, University of Liverpool).

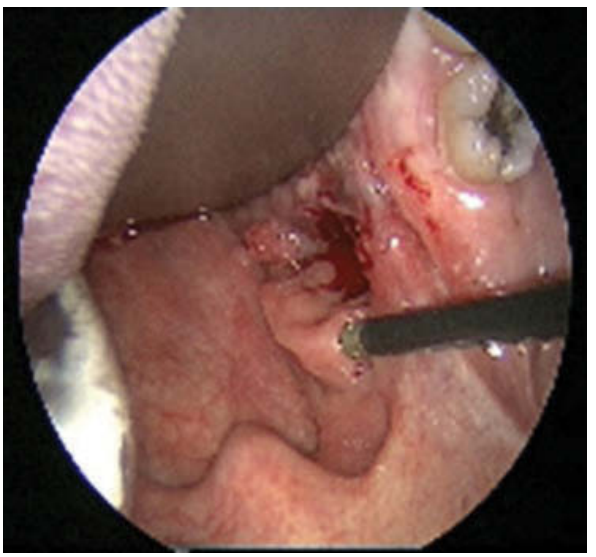

Figure 13.8 Intra-operative photograph of a T2 carcinoma of the right tonsil.

asymptomatic and patients present with cervical lymphadenopathy. They are also the most common site of primary tumours in the context of carcinoma of unknown primary origin (CUP).

As they enlarge, tonsillar tumours extend outside the confines of the tonsillar fossa. Their direction of local extension is unpredictable but can be cranial and medial onto the soft palate, caudal into the tongue base, posterolateral across the posterior pharyngeal wall, anterosuperior towards the retromolar trigone or laterally to involve the pterygoid musculature and other closely related structures in the neck, such as the carotid sheath. Disease which extends laterally and inferiorly may totally envelope the carotid sheath becoming contiguous with involved cervical lymph nodes. The extent of the local extension will obviously dictate the presenting symptoms which will range from being totally asymptomatic to having severe and intractable pain, often referred to the ipsilateral ear.

Base of tongue (BOT) make up ~30% of all OPSCC tumours. As with tonsillar OPSCC it is not unusual for BOT tumours to be asymptomatic or apparently occult, only coming to light during investigation of enlarged cervical lymph nodes. Local extension is typically towards and across the midline as well as into the intrinsic and extrinsic musculature of the tongue. Inevitably the greater the local extension the more likely symptoms relating to the tumour will be evident. Such symptoms can include odynophagia, persistent pain, including referred otalgia, dysphagia, altered speech, impaired tongue movement and bleeding.

Tumours of the oral surface of the soft palate make up the majority of the remaining 10% of OPSCC with posterior pharyngeal wall tumours presenting relatively rarely.

Soft palate OPSCC may present as a painful ulcerative lesion. Progression will result in involvement of the nasal surface of the soft palate, the superior tonsillar pole and/or the hard palate. These tumours not untypically present

as relatively small primary tumours with bilateral cervical lymphadenopathy. They are more likely to be HPV compared with OPSCC of the tonsil and BOT and accordingly typically behave in a more aggressive fashion with poorer outcomes.[3, 43]

Posterior pharyngeal wall tumours, which are also more likely to be HPV-, typically present late with symptoms of odynophagia, persistent sore throat and / or referred otalgia or dysphagia. They are notorious for presenting with widespread submucosal spread in all directions and as such are often underestimated on initial clinical assessment. The potential space between the pharyngobasilar and prevertebral fascia often acts as a barrier to deep spread and so tumour fixation as a consequence of deep spread to involve the prevertebral fascia is a very poor prognostic sign.

Patients presenting with oropharyngeal carcinoma present, broadly, in one of three ways:

- With symptoms related to the primary tumour with an enlarged cervical lymph node(s) which is/are usually painless and present at lymph node level II.
- With symptoms related to the primary tumour in the absence of an enlarged cervical lymph node(s) which is/are usually painless and present at lymph node level II.
- With an enlarged cervical lymph node(s) (usually painless and at level II) in the absence of symptoms related to a primary tumour (CUP).

It is well recognized that the presentation of patients with HPV+OPSCC differs significantly from the presentation of HPV-OPSCC.

HPV+OPSCC typically, although not exclusively, presents with a small primary tumour with multiple, enlarged, cystic cervical lymph nodes with a high prevalence of extracapsular spread (ECS). In contrast, HPV-OPSCC presents as a more typical head and neck cancer with larger primary tumours and relatively lower tumour burden in cervical lymph nodes.[6, 44, 45]

Symptoms relating to the primary tumour (soft palate, palatine tonsil, BOT or posterior pharyngeal wall) may vary quite considerably.

It is not unusual for patients to present with quite sizeable tumours in the absence of any obvious symptoms. In this patient group the primary tumour may be discovered incidentally following self-inspection or inspection of the mouth and oropharynx by a general medical or general dental practitioner, often in the context of seeking advice following a newly discovered neck lump. This is particularly the case for exophytic tumours of the palatine tonsil or BOT which have not invaded underlying musculature.

In contrast, ulcerative lesions which may be relatively small, may present initially with a sensation of sore throat with odynophagia. Larger lesions particularly of the BOT, posterior pharyngeal wall and tonsil may present with continuous pain exacerbated on swallowing and associated with referred otalgia and even dysphagia.

Incidental discovery of a painless enlarged cervical lymph node(s) whilst engaged in a routine task such as shaving or showering is a very common presentation for patients with OPSCC, especially HPV+OPSCC. If solitary, the presenting lymph node is almost invariably situated in lymph node level II whilst multiple lymph nodes will present typically as a chain extending from lymph node level II through III and IV, depending on the number and size of involved lymph nodes.

The presence of contralateral lymph nodes is not uncommon, especially if the primary tumour originates from the midline soft palate, midline BOT or midline posterior pharyngeal wall or is a non-lateralized tumour of the tonsil or BOT (i.e. a tumour encroaching or crossing the midline).

CLINICAL EXAMINATION

Oral cavity, pharynx and larynx

For patients presenting with signs and symptoms of an oropharynx cancer, a thorough examination of the head and neck should be undertaken as similar symptoms may result for tumours arising in one of several different anatomical sites of the upper aerodigestive tract (UADT).

The oral cavity should be carefully examined with the aid of a good light and tongue depressors. Inspection should include the buccal mucosa and lips, the palate, the tongue and floor of the mouth, all surfaces of the teeth and gums, opening and closing of the mouth and dental occlusion. Patients should be asked to elevate the tongue to the roof of the mouth and protrude the tongue towards both the right and the left. If tolerated by the patient, gentle intraoral palpation may be required to examine any swellings – this is particularly pertinent if a tumour of the BOT or tonsil is suspected as it is not unusual for tumours at these sites to be predominantly submucosal. Intraoral palpation may be combined with extra-oral palpation of the submental and submandibular lymph nodes and salivary glands to aid the characterization and/or localization of any swelling detected.

Following examination of the oral cavity, the oropharynx is then inspected with the tongue depressor placed firmly onto the dorsum of the tongue to depress it maximally. The anterior and posterior faucial pillars, the tonsil, retromolar trigone and posterior pharyngeal wall should all be inspected for colour changes, ulceration and swelling.

Pain and trismus arising as a consequence of pharyngolaryngeal or neck pathology may add to the difficulty of the examination but are significant clinical findings in their own right.

Following this initial inspection of the oral cavity and oropharynx, examination with a flexible fibre-optic endoscope passed through the nose, with or without topical anaesthesia, is essential. This will facilitate a high-resolution examination of the entire nasopharynx, oropharynx, larynx and often the hypopharynx. A camera attached to the endoscope permits the taking of high-quality photographs to record and present pertinent clinical findings.

Apart from the clinical scenario of an apparent CUP, an oropharyngeal tumour is usually readily detectable on clinical examination.

The neck

Even in the absence of an obvious neck node, it is essential to undertake a thorough examination of the neck if an oropharyngeal carcinoma is suspected. In order to do this the patient should be examined in the sitting position with the whole neck exposed so that both clavicles are clearly seen. The neck is inspected from the front and the patient asked to swallow, preferably with the aid of a sip of water. Movements of the larynx and any swelling in the neck are noted. The neck is then examined from behind with the chin flexed slightly downwards to remove any undue tension in the strap muscles, platysma and sternocleidomastoid muscles.

On examination for a lump in the neck, it is often helpful to ask the patient to point to any lump they have noticed first. Ask if the lump is tender. The neck is palpated bilaterally in a sequential manner comparing the two sides of the neck. All five palpable neck node levels (I-V) should be examined systematically as well as parotid and pre- and post-auricular nodes.

If a node is clinically obvious, either on inspection or on palpation, clinical examination should concentrate on ascertaining whether the node is solitary or whether there are multiple enlarged lymph nodes prior to estimating their size, determining their consistency (and whether they trans illuminate) and finally, whether they are mobile and therefore, by inference, amenable to surgical resection.

INVESTIGATIONS

1. **Patients presenting with a clinically evident primary tumour and an enlarged cervical lymph node(s) require the following investigations:**
   a. Ultrasound imaging of both sides of the neck followed by ultrasound guided fine-needle aspiration cytology (FNAC) of any neck nodes which are suspicious, on size and/or morphological criteria, of being involved with metastatic disease.
   b. Cross-sectional imaging (CT or MR) of the head and neck. Which imaging modality is employed is usually decided on the basis of local multidisciplinary team (MDT) preferences.
   c. A CT scan (or PET-CT scan) of the thorax and upper abdomen, in order to establish the absence (or presence) of a synchronous primary bronchogenic carcinoma or pulmonary and/or hepatic distant metastases.
   d. An examination under anaesthesia (EUA) of the UADT including a biopsy of the presenting primary tumour.

      Occasionally, it may be possible to biopsy an exophytic oropharyngeal tumour in the outpatient setting. Despite this, an EUA is still recommended if there are no contraindications in order to assess fully the extent and potential operability of the primary tumour.
2. **Patients presenting with a clinically evident primary tumour in the absence of enlarged cervical lymph nodes require the following investigations:**
   a. Cross-sectional imaging (CT or MR) of the head and neck. Which imaging modality is employed is usually decided on the basis of local MDT preferences.
   b. A CT scan (or PET-CT scan) of the thorax and upper abdomen, in order to establish the absence (or presence) of a synchronous primary bronchogenic carcinoma or pulmonary and/or hepatic distant metastases.
   c. An EUA of the UADT including a biopsy of the presenting primary tumour.

      As above, occasionally, it may be possible to biopsy an exophytic oropharynx tumour in the outpatient setting. Despite this, particularly if surgery is a treatment option and as long as there is no contraindication, an EUA is still recommended in order to assess fully the extent and operability of the primary tumour.
3. **Patients presenting with a clinically occult primary tumour with a clinically N+ neck (CUP), require the following investigations:**
   a. Ultrasound imaging of both sides of the neck followed by ultrasound guided FNAC of any neck nodes suspicious, on size and/or morphological criteria, of being involved with metastatic disease. This will, in most cases, confirm the diagnosis of metastatic SCC. If sufficient material is available, HPV testing of FNAC specimens is increasingly being advocated as detection of HPV in an enlarged metastatic cervical lymph node, strongly indicates that the primary site will be in the oropharynx – in particular the tonsil or BOT.[46, 47]
   b. In the absence of evidence of an obvious primary tumour on clinical examination, cross-sectional imaging (CT or MRI) of the head and neck is the usual next investigation of choice in many head and neck cancer centres.

      If the MRI scan confirms the presence of an obvious primary tumour then further investigation may proceed as outlined above with
   c. A CT scan (or PET-CT scan) of the thorax and upper abdomen, in order to establish the absence (or presence) of a synchronous primary bronchogenic carcinoma or pulmonary and/or hepatic distant metastases followed by
   d. An EUA of the UADT including a biopsy of the presenting primary tumour.

If, however, the MRI or CT scan of the head and neck does not delineate a likely primary tumour, then instead of proceeding with a CT scan of thorax and upper abdomen, a whole body PET-CT scan is the investigation of choice as has greater sensitivity for detecting primary tumour site,

whilst simultaneously investigating the presence of distant metastases.

If the PET-CT identifies, on the basis of increased FDG uptake, a likely primary site then and EUA should take place, to enable targeted examination and biopsy of the putative primary site.

In contrast, if PET-CT fails to identify a putative primary site an EUA should still be undertaken to allow a detailed inspection of the UADT taking particular note of the ipsilateral tonsil and BOT as these are the most likely sites of a small primary tumour. In the absence of an obvious primary tumour of the tonsil or BOT, the ipsilateral post nasal space and piriform fossa should be inspected.

If a primary tumour is still not revealed, at least the ipsilateral tonsil should be removed and either biopsies or a formal mucosectomy of the ipsilateral BOT should be performed and sent for histological assessment. Some clinicians would also advocate taking biopsies of the mucosa of the fossa of Rosenmüller and the ipsilateral piriform fossa.

Removal of the contralateral tonsil +/- a contralateral BOT mucosectomy is advocated by some clinicians.[48–50] However, this is a subject of much debate which revolves around the likelihood of detecting a tumour in the contralateral tonsil or tongue balanced against the morbidity of the procedures. To date, robust data do not currently exist to mandate this approach.

In all cases, biopsy of primary site tumours should be subjected to HPV testing. At the very least, this should involve immunohistochemistry for $p16^{INK4a}$ overexpression as described above as this has prognostic significance. If, however, as part of a clinical trial, de-intensified treatment is an option, then serious consideration should be given to additional testing for HPV DNA as outlined in the diagnostic algorithm above. Taking this dual testing approach minimizes the risk of de-intensifying treatment for the small proportion of patients who have tumours which overexpress $p16^{INK4a}$ but which are, in fact, HPV-.

Ultrasonography +/– fine needle aspiration cytology of a cervical lymph node

High-resolution ultrasound scanning (USS) has an established role in the contemporary management of head and neck cancer as the enumeration and characterization of cervical lymph nodes which contain metastatic tumour has a profound impact on outcome. It is common for USS +/- FNAC to be offered as part of a 'one-stop' neck lump diagnostic service in many head and neck centres.[51, 52]

Although USS and FNAC are operator-dependent and therefore should only be undertaken by specialists in the technique, it has been established that USS is more sensitive than palpation in the detection of enlarged cervical lymph nodes (97% vs 73%) and provides high specificity when combined with FNAC in the diagnosis of nodal metastases (93%). Moreover, ultrasound-guided FNAC is more accurate than non-image-guided FNAC.[53]

Magnetic resonance imaging (MRI)

MRI is used in many centres as the primary imaging modality of the head and neck. Continued development of MRI software and hardware ensure the ongoing improvement in MRI to distinguish pathology from normal anatomy. MRI is performed according to defined sequences. Three sequence parameters form the basis of head and neck imaging. T1-weighted images provide a high degree of spatial resolution of normal anatomy. T2-weighted images in contrast preferentially detect water content and therefore pathology. A short tau inversion-recovery (STIR) sequence also preferentially detects water content but in addition, suppresses the fat content of adjacent tissue to further enhance the contrast of pathological lesions. Intravenous gadolinium enhances the imaging of the vascular attributes of a tumour which adds to the contrast of a STIR sequence which may be of particular advantage when imaging apparently occult disease (**Figure 13.9**).

Accordingly, the soft tissue contrast features of MRI are superior to CT and therefore, in the absence of any contraindications (for e.g. inability to tolerate the increased scanning duration and/or intolerance to gadolinium), MRI is the preferred imaging option for oropharynx pathology.

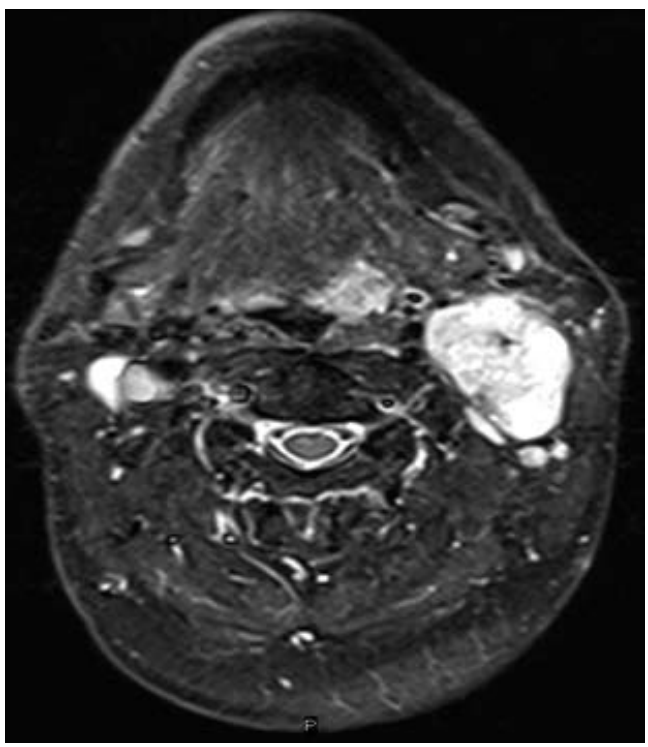

Figure 13.9 An axial short tau inverted-recovery (STIR) sequence magnetic resonance image (MRI) of a T2N2b carcinoma of the left base of tongue.

Computed tomography (CT)

Despite the widespread use of MRI in the staging of locoregional disease volume, CT is possibly the mainstay imaging modality for head and neck disease in most centres as it is widely available and its use in the staging of head and neck cancer is firmly established. It also facilitates imaging of the head and neck at one sitting which has obvious advantages for the patient and healthcare provider. Current imaging protocols ensure that imagine acquisition is rapid thereby reducing movement artefact as well as providing an advantage for patients unable to tolerate the more prolonged imaging sequence required for MRI. It is preferable to MRI if bone imaging is required but soft tissue resolution, particularly when staging soft tissue tumour extent, is comparatively inferior. Contrast-enhancement, using iodine-based contrast medium, based on a more rapid opacification of normal soft tissue than tumour provides added discrimination between tumour and normal. Contrast enhancement is contraindicated in patients with renal impairment. Contemporary CT software allows the high-resolution reconstruction of images to provide highly detailed 3D reconstruction which may be of considerable value when planning bony cuts, resection or reconstruction. The main downside of CT is the significant radiation dose incurred.

Positron emission tomography combined with CT (PET-CT)

The principle upon which this technique is based is the differential uptake, by cancer cells, of various labelled tracers, the pattern of which can then be fused with conventional CT images to create a functional map of the tumour. 18 fluoro-deoxyglucose (18-FDG) is the most commonly used tracer in clinical practice. Cancer cells rely preferentially on glycolysis, rather than aerobic respiration, for energy production (the Warburg effect). Accordingly, glucose derivatives, including 18-FDG, are preferentially transported into malignant cells and trapped. This differential transport is not exclusive to cancer cells as uptake is also greater in metabolically active cells such as inflammatory cells or active muscle. In light of this, PET-CT has to be undertaken in a quiet environment, when the patient is relaxed and preferably prior to the taking of diagnostic biopsies. Despite these precautions, PET-CT has a relatively low specificity with a high false-positive rate.[54, 55] Following administration and uptake, the labelled glucose tracer is detectable with a gamma camera. Metabolic activity is then accurately co-registered with the anatomical location defined by the CT images, thereby creating the functional map. In the context of OPSCC, PET-CT is most commonly used in the context of CUP, as recommended in the UK Royal College of Radiologists Guidelines published in 2013 (**Figure 13.10**).[56]

Examination under anaesthesia (EUA)

An EUA is highly recommended for all patients presenting with OPSCC, even if the primary tumour is evident on clinical examination in the outpatient department. The aims of EUA are typically threefold.

- To take a diagnostic biopsy of the primary tumour, and/or to assess the presence of a primary tumour in cases where a primary tumour is not immediately evident on clinical examination in the outpatient department.
  (A biopsy of the primary tumour is essential for subsequent treatment planning – surgical or non-surgical – even if a positive FNAC diagnosis of a cervical lymph node has been previously obtained. Only in the relatively rare cases when an EUA is contraindicated (usually on the basis of patient fitness) should treatment proceed on the basis of an FNAC result alone.)
- To assess the locoregional extent of the tumour and its relationship to adjacent anatomical structures. This is particularly pertinent if surgery is being considered.
- To exclude the presence of a synchronous second primary tumour.

Following anaesthetic induction, the patient is placed in a supine position with the neck extended assuming there is no contraindication. The sequence of events may vary depending upon operator preference but the following steps are mandatory.

1. Palpation of the BOT and vallecula if access is possible as well as palpation of the lateral walls of the oropharynx and postnasal space.

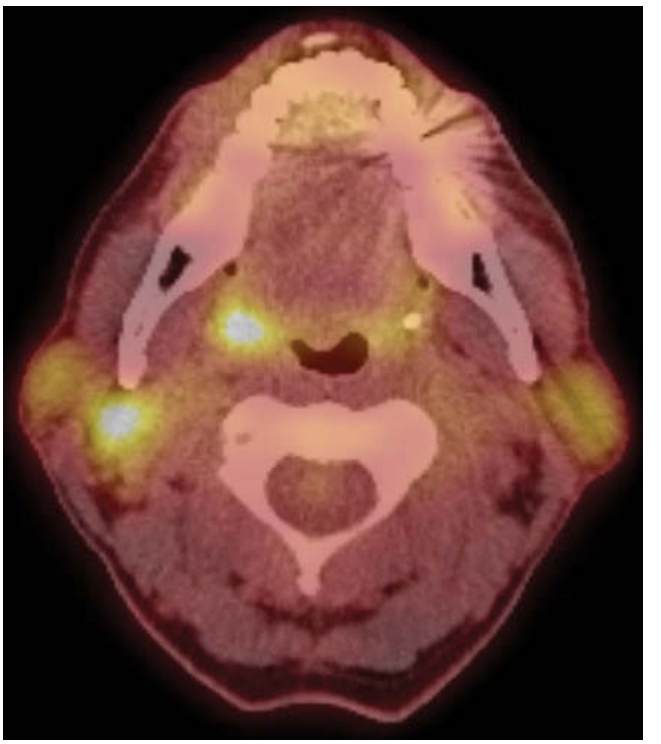

Figure 13.10 A fused axial section of an 18-fluoro-deoxyglucose (18-FDG) PET-CT scan showing increased 18-FDG uptake in the left tonsil and a left metastatic cervical lymph node.

2. An examination of the hypopharynx and cervical oesophagus, using rigid pharyngoscopes +/– a rigid fibre-optic light source.
3. A direct or rigid fibre-optic light source-assisted laryngoscopy.
4. Visual inspection of the oropharynx using an oropharyngeal gap and headlight.
5. A biopsy of any obvious or suspicious primary tumour.

Tonsil biopsy versus diagnostic tonsillectomy

If a primary tumour of the tonsil is evident then it is sufficient to take a representative biopsy to establish histological diagnosis.

If, however, following examination, it is considered that a likely primary tumour is contained within one tonsil a potential dilemma exists, particularly if transoral surgery is a primary treatment option. Traditional teaching would dictate that a diagnostic tonsillectomy is undertaken. However, this may compromise the reporting of surgical margins, complicate revision transoral surgery and adjuvant treatment decision-making. If transoral surgery is a primary treatment option then it may be preferable to either i) simply taking a representation diagnostic biopsy from the centre of the tonsil, avoiding the margins or ii) performing a tonsillectomy according the principles of TLM or TORS surgery. Adopting the former approach ensures that subsequent transoral surgery is not compromised whilst adopting the latter approach ensures that a diagnostic biopsy and appropriate resection are undertaken at the same time and adjuvant treatment decision making is not compromised.

In a third scenario, on EUA of a patient presenting with CUP, if the ipsilateral tonsil appears normal, undertaking the tonsillectomy according to TLM or TORS principles ensures that resection is appropriately completed in the context of a primary tumour being diagnosed on subsequent histological examination and appropriate adjuvant treatment decision-making can proceed unhindered following the completion of an ipsilateral selective neck dissection on a separate occasion.

STAGING

The staging of head and neck cancer will be dealt with in detail in Chapter 4, Staging of head and neck cancer. However, it is worth highlighting recent changes to the TNM staging recommendations published in the American Joint Committee on Cancer (AJCC) Cancer Staging Manual 8th edition[45] and the Union for International Cancer Control (UICC)[57] which are of particular importance to the staging of OPSCC. The changes and the rationale behind them are reviewed in detail in Lydiatt et al.[47]

1. In contrast to the AJCC 7th edition which considered staging of cancers of the naso-, oro- and hypopharynx in one chapter, the AJCC 8th edition divides pharyngeal cancers into three separate chapters which consider the staging of nasopharynx, p16+HRHPV associated OPSCC (p16+OPSCC)* and p16–non-HRHPV associated OPSCC (p16–OPSCC) together with hypopharynx cancers.
2. In the 8th edition, T stages for p16+OPSCC and p16–OPSCC remain the same apart from two exceptions for p16+OPSCC.
   a. The Tis classification has been removed because a premalignant lesion has yet to be identified in p16+OPSCC and because of the absence of a basement membrane in Waldeyer ring epithelium, the presence of which is essential for a diagnosis of Tis.
   b. T4b has been removed as the outcomes for T4a and T4b categories are indistinguishable when considering p16+OPSCC. Consequently a single T4 category remains in the 8th edition.
3. A T0 category is no longer assigned to p16–OPSCC and other non-HRHPV cancers for example larynx, oral cavity and hypopharynx as an exact primary site is, by definition, unable to be established and therefore cannot be assigned to a specific anatomical subsite. In contrast, cytology specimens following FNAC of an enlarged lymph node in which the presence of metastatic carcinoma is confirmed can be subjected to testing for HPV and Epstein—Barr virus (EBV) status. (In this context and in contrast to the recommendation above, both HPV ISH and p16 overexpression is necessary for the confirmation of HPV status whilst the presence of Epstein Barr Encoded RNA (EBER) determines EBV association.)

   It is considered that demonstration of HPV status or EBV status safely allows the primary site to be determined as oropharynx or nasopharynx respectively and therefore, classification systems for p16+OPSCC and nasopharynx maintain T0 categories. (As does salivary gland because primary site can be determined on cytological findings).
4. As p16+OPSCC may be treated with primary surgery or primary RT +/– chemotherapy, separate clinical and pathological staging systems have been stipulated.
   a. The clinical, or cTNM, classification is designed for patients before treatment (regardless of the intended form of treatment) and employs information from physical examination and imaging.

* Importantly and contentiously, HPV status determined according to the diagnostic algorithm described earlier in the chapter is not mandated as HPV-ISH is not widely available in centres throughout the world and its interpretation is often difficult. Instead, p16 overexpression as assessed by immunohistochemistry (>75% expression with at least moderate staining intensity) is considered sufficient to allow re-classification of OPSCC into p16+HRHPV associated OPSCC (p16+OPSCC) and p16 – non-HRHPV associated OPSCC (p16–OPSCC).

In this classification system, the presence of one or multiple involved ipsilateral cervical nodes, all < 6 cm, is classified as N1. The presence of bilateral or contralateral involved nodes < 6 cm, is classified as N2, whilst the presence of any node > 6 cm is classified as N3.

b. The pathological, or pTNM classification is designed only to patients managed with primary surgery. When surgical data were considered, lymph node size, even > 6 cm, or the presence of bilateral or contralateral lymph nodes was not discriminatory. Instead, the number of involved lymph nodes appeared critical. Accordingly, the presence of one to four lymph nodes is classified as N1 whilst five or more positive lymph nodes of any size are classified as N2.

Why the presence of lymph nodes > 6 cm is discriminatory in cTNM staging but not pTNM staging is not clear.

5. Consideration of T and N staging together has led to the publication of three separate stage groupings for OPSCC: separate clinical and pathologic groupings for p16+OPSCC and combined clinical and pathologic groupings for p16−OPSCC. The separate p16+OPSCC clinical and pathologic stage groupings each have three categories (I, II, III and IV) whilst the p16−OPSCC combined clinical and pathological stage grouping has six categories, as per the 7th edition, (I, II, III, IVA, IVB and IVC). Stage II and IVC are reserved for the presence of distant metastatic disease in each classification respectively.

It is important to stress that although the TNM 8th edition is useful for prognostication currently, it should not be used to inform treatment decision-making as its role in treatment allocation requires prospective evaluation in randomized clinical trials or similarly robust studies. Therefore, the management principles for OPSCC described in subsequent chapters have not been modified for TNM 8th edition.

MANAGEMENT

The management of oropharyngeal carcinoma represents an increasing clinical challenge, both because of its rising incidence, particularly in younger patients as a result of HPV infection, and because of the significant technological advances that have occurred in radiotherapy and surgery over the last 10–20 years which have increased treatment options for patients, with little robust evidence yet of their relative merits.

This situation is further complicated by the clinical paradox that has been created following the emergence of HPV+OPSCC. HPV status is highly prognostic in OPSCC patients treated with CRT. In a landmark study, Ang et al retrospectively analyzed the outcomes of patients with stage III/IV OPSCC treated with CRT in the RTOG 0129 study by HPV status: 3-year overall survival was 82.4% in HPV+patients, compared to 57.1% in HPV-patients ($p < 0.001$). Similarly high survival rates for HPV+OPSCC have been demonstrated in patients treated with primary RT/CRT and surgery.[7, 24, 58–62]

However whilst patients with HPV+OPSCC, in general, do better in survival terms than patients with HPV-OPSCC, it must also be borne in mind that a sub-set of patients with HPV+OPSCC also do badly. Whilst high T-stage and number of involved lymph nodes are associated with poor outcome in this subgroup, smoking habit, which is assumed to be a surrogate of underlying tumour mutational load and / or genetic instability, also appears to be of importance.[6, 7, 43]

Currently HPV+ and HPV- OPSCC are managed according to the same treatment protocols, but the improved prognosis associated with HPV-positivity has raised the possibility that they could be managed differently. In particular, there is a need to continually strive for novel intensified treatments which will enhance survival in patients with HPV-OPSCC and the subgroup of patients with HPV+OPSCC who will do badly, whilst potentially considering de-intensified treatment strategies for patients with HPV+OPSCC who will do well, with the aim of maintaining their current good survival outcomes whilst reducing the frequency and severity of short- and long-term post-treatment adverse events.

There is an absence of randomized studies comparing primary surgical and non-surgical approaches in the management of OPSCC, resulting in a global lack of consensus between surgeons and oncologists as to how these cancers should be managed. The options are:

- For T1-T2 N0: Radical radiotherapy or transoral surgery and neck dissection(with post-operative (chemo) radiotherapy if there are adverse pathological features on histology).
- For other stages: primary CRT or surgery and adjuvant (chemo) radiotherapy.

Open surgery and microvascular reconstruction followed by post-operative adjuvant treatment was the historic treatment of choice for OPSCC and is still offered by some units. However, a 2002 retrospective review of 6400 patients with OPSCC in 51 studies showed similar rates of locoregional control, overall survival and cause-specific survival for patients treated with open surgery and post-operative RT (PORT), compared with those treated with primary RT +/− neck dissection, but a significantly higher rate of severe or fatal complications in the surgery group, together with worse functional outcomes.[63] These data raised concerns regarding the continued use of this approach and when combined with high-quality level I and meta-analysis data confirming that benefit of radiotherapy +/− cisplatin-based chemotherapy[7, 64] in the management of OPSCC, a major shift away from open surgery to CRT in the developed world has occurred.

This shift is reflected in UK data from successive National Head and Neck Cancer (DAHNO) audits which confirm that by the 10th audit, CRT was given more than twice as frequently as RT alone.[65] Similarly, data from the US has shown a linear rise (from 20% to > 60% of cases) in the use of CRT for the management of OPSCC from

1998 to 2009 with a concurrent decrease in the use of surgery and radiotherapy alone.[66]

Radiotherapy (RT)/concurrent chemoradiotherapy (CRT)

The primary rationale for the use of RT or CRT in treating OPSCC is organ preservation and also, importantly, to preserve function whilst achieving high cure rates. Data from randomized trials, such as RTOG 0129,[67] comparing CRT schedules confirm that this approach can result in good oncological outcomes, particularly in HPV+ OPSCC. However, it is worth reiterating that high-quality data comparing surgical and non-surgical approaches do not exist, despite RT and CRT becoming the accepted standard of care in many centres throughout the world for early and late stage OPSCC respectively.

Early stage T1-T2 N0-N1 OPSCC can be effectively treated with RT alone.[68] For radical treatment, RT is commonly delivered at a total dose equivalent of 70 Gy in 35 fractions and this may be delivered as a hypofractionated schedule of 65–66 Gy in 30 fractions.

For more advanced T and/or N stage (stage III/IV, TNM 7th edition) OPSCC, CRT is the standard of care, with a RT dose equivalent of 70 Gy delivered in 35 fractions together with concurrent cisplatin at a dose of 100 mg/m^2 given on days 1, 22 and 43 of the RT schedule. The GORTEC 94-01 study demonstrated a ≥20% 3- and 5-year survival benefit for the addition of chemotherapy to RT, albeit in the setting of low overall survival figures (3-year overall survival 51% vs 31%, p = 0.02, disease-free survival 42% vs 20%, p = 0.04 and locoregional control 66% vs 42% p = 0.03).[69] Furthermore, meta-analysis data in 17 346 patients confirmed that, for HNSCCs as a whole, concurrent chemotherapy confers an overall survival benefit of 6.5% at 5 years (p < 0.0001), compared to RT alone.[64] The benefit of adding chemotherapy to RT for the management of OPSCC specifically was confirmed in an additional systematic review.[70]

Weekly administration of low-dose cisplatin (40–50 mg/m^2) is an alternative to 3-weekly high-dose cisplatin which has become increasingly used in clinical practice in an attempt to improve tolerance and compliance. A recent meta-analysis of 4209 patients in 52 studies concluded that there was no difference in treatment efficacy, as measured by overall survival or response rate, between the low-dose weekly and high-dose 3-weekly cisplatin regimens.[71] The weekly regimen was associated with a higher compliance rate and was significantly less toxic with regards to severe (grade 3–4) myelosuppression, nausea and nephrotoxicity. The authors concluded that the weekly regimen needed to be prospectively compared with the standard 3-weekly regimen before being adopted into routine clinical practice. In the meantime, clinicians will continue to choose between regimens, based on institutional protocols, personal experience and patient fitness. In patients for whom cisplatin is contraindicated, concurrent carboplatin chemotherapy (3-weekly at area under the curve (AUC) 5 or weekly at AUC 2) is an alternative that is associated with less ototoxicity and nephrotoxicity.

Concurrent weekly cetuximab (a monoclonal antibody targeting the epidermal growth factor receptor (EGFR) may be given with RT if there is a contraindication to platinum chemotherapy. In a randomized trial, the combination of cetuximab and RT improved median locoregional control (24.4 vs 14.9 months) and median duration of overall survival (49 vs 29.3 months) after a median follow-up of 54 months[72] and this survival difference was maintained on long-term follow-up. The addition of cetuximab to concurrent CRT did not improve outcome compared to CRT alone in a subsequent trial.[73] The results of randomized studies conducted in the USA (RTOG 1016: NCT01302834) and UK (DE-Escalate: NCT01874171) comparing the efficacy and toxicity profile of RT with concurrent cisplatin vs RT with concurrent Cetuximab in HPV+OPSCC are awaited and may change the future standard of care for the non-surgical management of this disease.

Radical RT may be given alone for patients with advanced disease who are not fit for concurrent treatment, particularly if >70 years of age when the benefits of concurrent chemotherapy and cetuximab are reduced.

Induction (or neoadjuvant) chemotherapy

The use of induction chemotherapy (IC) may be beneficial in selected patients. The MACH-NC meta-analysis[64] showed an overall survival advantage for cisplatin and 5-FU chemotherapy compared to local therapy alone for the management of HNSCC, and IC had a relatively more pronounced effect on distant metastasis rate than concurrent CRT. The benefits of using IC prior to concurrent cisplatin-based CRT have not been convincingly shown: a recent meta-analysis which included all types of HNSCC showed that IC increases toxicity and does not improve OS compared to CRT alone.[74]

In the context of OPSCC, including HPV+OPSCC, the use of IC has been advocated for patients with advanced (T4, N3, N2c) disease to reduce the risk of distant metastases.[44] High-quality prospective evidence of its efficacy in these indications is currently not available.

IC with the TPF regimen (taxotere, cisplatin and 5-FU) is recommended, based on a higher response and survival rates and reduced locoregional and distant failure rates compared to PF (cisplatin and 5-FU) in a meta-analysis of five studies.[75] The regimen is associated with higher acute toxicity (neutropenic sepsis and non-haematological toxicities) and therefore is only suitable for patients with good performance status and minimal comorbidity.

Radiotherapy planning and delivery

PRE-TREATMENT EVALUATION

All patients should undergo the following assessments before starting RT:

- **Dental assessment:** including orthopantomogram (OPT) for dentulous patients if the upper or lower jaw is likely to be in the radiation field. Dental treatment,

particularly extraction, should be carried out prior to starting RT (ideally 2 weeks before) to reduce the risk of osteoradionecrosis.

- **Nutritional assessment:** dietetic input prior to the start of treatment is important to start patients with pre-existing weight loss (>10%) on supplementary feeding prior to treatment and to identify patients who are likely to require a feeding tube to support their nutritional requirements during and after treatment. The choice between feeding gastrostomy tube (proactive or reactive) or nasogastric tube depends upon local preference, expertise and availability of resources.
- **Speech and swallowing assessment:** to assess speech and swallowing function and educate patients on proactive swallowing exercise to be repeated daily prior to and during treatment in order to minimize swallowing difficulties in the short and long term.

RADIOTHERAPY PLANNING

Intensity-modulated radiotherapy (IMRT) is now the accepted standard of care for RT treatment planning and delivery for OPSCC (**Figure 13.11**) – the conformal dose distributions achieved allow sparing of normal tissues and organs at risk, potentially reducing toxicities and improving quality of life (QOL). The UK phase III PARSPORT study demonstrated that parotid-sparing IMRT reduces the incidence of grade 3–4 xerostomia (dry mouth) compared to conventional RT, from 83% to 29% 24 months after treatment ($p = 0.0001$).[76]

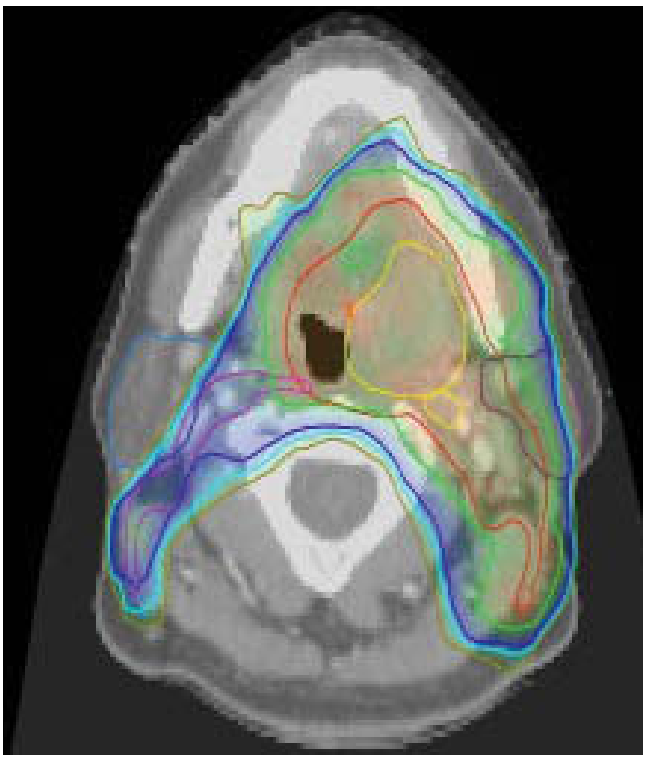

Figure 13.11 Intensity-modulated radiotherapy (IMRT) plan for left tonsillar carcinoma. Gross tumour volume (GTV) for left tonsillar primary and retropharyngeal node (yellow): Clinical target volume (CTV1) for radical dose RT (red): CTV2 for prophylactic dose RT (purple): 62.7 Gy, 51.3 Gy and 48 Gy isodose lines (shown in green, blue and mustard respectively).

Intensity modulation is delivered using a step and shoot technique or more recently, with dynamic arc therapy, either volumetric modulated arc therapy (VMAT) or tomotherapy.

Prior to target volume delineation, the primary tumour should be defined as lateralized or non-lateralized, depending on the site of the primary, T stage and extent of involvement of midline structures, as follows:

Lateralized tumour: tumour confined to the tonsillar fossa/lateral pharyngeal wall extending onto or into the adjacent BOT and/or soft palate by < 1 cm and with > 1 cm clearance from midline.

Non-lateralized tumour: tonsillar/lateral pharyngeal wall tumour that involves the adjacent BOT and/or soft palate by ≥ 1 cm or with ≤ 1 cm clearance from midline.

OR

A tumour that arises from a midline structure (BOT, soft palate or posterior pharyngeal wall primary tumour).

This will determine whether contralateral neck irradiation is required in cN0 cases (see 'Management of the neck' below).

Target volume definition

Patients will require a custom-made thermoplastic immobilization shell to ensure a reproducible position for accurate radiotherapy delivery. A 5-point immobilization system is normally used which includes the head, neck and both shoulders. Target volume delineation is carried out on a contrast-enhanced planning CT scan, often co-registered with the staging MRI and/or PET scan to enhance target volume definition. Target delineation requires a detailed knowledge of cross-sectional anatomy as well as detailed knowledge of tumour location and extent from the staging investigations. The following volumes are defined:

Gross tumour volume (GTV): the primary tumour (GTVp) and involved lymph nodes (GTVn) are delineated.

Clinical target volume (CTV): the CTV is a margin for microscopic disease and is usually divided into 2 or 3 volumes.

CTV1 (the high-dose CTV): typically, CTV1 includes a 1 cm isotropic margin around the primary and nodal GTVs and the whole of the involved nodal level in the neck. The isotropic margin may vary from 0.5 cm to 1.5 cm depending on local protocols and the certainty with which a tumour can be defined from the staging investigations.

CTV2 (the intermediate dose CTV): an optional volume which may include the whole involved nodal level in the neck (if not included in CTV1) and/or an additional isotropic margin around CTV1.

CTV3 (the prophylactic dose CTV): includes the 'at risk' nodal levels. For node negative OPSCC, this typically includes levels II–IVa. For node positive OPSCC, this typically includes levels Ib–V(b or c).

Internationally agreed consensus guidelines for the delineation of at risk nodal levels are used to guide outlining of the prophylactic CTV.[77]

Planning target volume (PTV): a margin (typically 3–5 mm) that is automatically added by the planning system to ensure the CTV is adequately covered on every day of treatment.

Organs at risk, including the spinal cord, brain stem, parotid glands and swallowing related structures are also outlined and also given a planning margin called the **Planning risk volume (PRV)**.

Defining the objectives for target volume coverage and constraints for the organ at risk doses, as well as the relative priorities of each, is then required prior to inverse treatment planning.

TOXICITIES OF RT/CRT

Radiotherapy can result in significant acute (< 90 days) and late (> 90 days after treatment) toxicities and late toxicities, particularly affecting salivary gland function, dentition and swallowing, may be permanent. CRT increases the risk of late toxicity[78, 79] and in the pre-IMRT era, up to 43% of HNSCC patients could develop grade 3–4 late toxicities following CRT.[80] The key late toxicity affecting QOL is swallowing dysfunction.[81] Swallowing is a primary concern for patients,[82] affecting their physical health and well-being, and is a major cause of distress and burden for family members[83] since dysphagic patients often require long-term supportive care.

Whilst the PARSPORT study demonstrated reduced rates of xerostomia in patients treated with IMRT compared to conformal RT, late dysphagia can still be an issue, even in patients treated with IMRT. Feeding tube dependence, a crude measure of swallowing dysfunction, has been reported in 8.6% of OPSCC patients at 1 year and 4.4% at 2 years after modern chemo-IMRT in a multi-institution pooled analysis.[84] Furthermore, a significant deterioration in patient-reported impairment in swallowing function, measured using the MD Anderson Dysphagia Inventory (MDADI), score, is seen in most patients 12 months after treatment and a deterioration of at least 20 points is still detectable in 15% of patients 24 months after treatment.[85,86] Aspiration, which can result in life-threatening episodes of pneumonia, may arise as a consequence. A US study identified > 3500 patients > 65 years who had been treated with CRT for head and neck squamous cell carcinoma (HNSCC) from the SEER-Medicare database (2000–2009) – it showed that > 25% of OPSCC patients had experienced at least one episode of aspiration pneumonia 10 years after treatment.[87]

Late dysphagia correlates with mean radiation dose to the swallowing-related structures (pharyngeal constrictor muscles, glottic and supraglottic larynx, oral cavity and cervical oesophagus), with the correlation being highest for the superior pharyngeal constrictors.[88, 89] The normal tissue complication probability curve for the pharyngeal musculature is sigmoidal in shape and increasing mean radiation doses between 50 and 60 Gy are in the critical range for late dysphagia.[88] The potential of dysphagia-optimized IMRT to reduce dysphagia rates, by reducing radiation doses to swallowing-related structures, holds significant promise and is being prospectively evaluated by a number of investigators and in an ongoing UK randomized controlled trial (RCT) (DARS ISRCTN: 25458988). Omitting chemotherapy could also potentially reduce the risk of dysphagia in selected patients, as concurrent chemotherapy increases late dysphagia rates compared with IMRT alone[89] and, as outlined above, the results of studies comparing the use of cetuximab instead of cisplatin with RT, in the context of good prognosis HPV+OPSCC, are awaited. Furthermore, prospective studies to determine whether intensity modulated proton beam therapy (IMPT) can reduce toxicity compared to IMRT by sparing non-target tissue in the head and neck are being planned.

Post-operative (adjuvant) RT/CRT for OPSCC

Evidence for the role of adjuvant RT after (open) surgery in head and neck cancers was provided by the RTOG 73-03 trial which showed that post-operative RT improved local control.[90] Subsequent studies helped to establish the optimum dose of post-operative radiation and recommended a minimum dose of 57.6 Gy to the primary site with up to 63 Gy to areas of ECS.[91] Prophylactic treatment for microscopic disease was established by a study showing that a dose of 50 Gy in 25 fractions was sufficient to control microscopic disease in over 90% of cases.[92] Patients should start their post-operative RT as soon as possible after surgery, ideally within 5 weeks (35 days) and no later than 6 weeks (42 days) to avoid reduced local control and survival due to protracted treatment beyond a total of 11 weeks (for surgery and RT combined).[93]

The indications for post-operative RT and CRT for OPSCC depend on pathological risk factors for recurrence common to most HNSCCs. These include: primary tumour factors (close (1–5 mm) or positive (< 1 mm) margins, T3–4 stage, perineural and/or lymphovascular invasion) and nodal factors (ECS of nodal disease and/or N2-N3 nodal stage). RCTs conducted by the RTOG and EORTC and a meta-analysis of their results confirmed that patients with ECS and/or microscopically involved (< 1 mm) surgical resection margins around the primary tumour experience significant benefit in terms of overall and disease-free survival from post-operative CRT compared to RT alone.[94] However, post-operative CRT results in significant toxicities (including a 2% death rate) and is not generally recommended in patients > 70 years of age and/or those with significant co-morbidities and poor performance status.

Transoral surgery

In light of accumulating retrospective data of efficacy and following the FDA approval of TORS for the management of OPSCC, there has been a resurgent interest in the transoral surgical management of OPSCC, with a 4.4% increase in the use of primary surgery in the US between 2009 and 2012,[95] a trend that is only likely to continue.

Transoral laser microsurgery (TLM) and transoral robotic surgery (TORS) are minimally invasive surgical techniques for OPSCC, which have the potential to excise T1-T3 tumours with considerably less long-term functional deficit than open surgery. Transoral surgery (TOS) of the primary tumour is usually performed in conjunction with a neck dissection, either carried out at the same time, or as a staged procedure. Although early stage (T1-T2 N0-N1) OPSCC can be effectively treated with surgery alone,[62] adjuvant treatment is required in most patients, usually due to advanced nodal disease.

It is important to note that whilst TLM and TORS employ a transoral approach for tumour resection, there are important practical and philosophical differences between the techniques which is often not appreciated by the uninitiated. The most important difference is that whilst the technique of TLM dictates that the extent of surgery, in an attempt to minimize the removal of uninvolved tissue adjacent to the tumour, is governed by the specific anatomy of the tumour and so differs from case to case, TORS is predicated on the advisability of undertaking a standard procedure avoiding transtumoral resection and attempts to adhere to the principles of traditional *en bloc* surgical resection.

Transoral laser microsurgery (TLM)

(For more information regarding the role of TLM in general, please see Chapter 22, Transoral laser microsurgery)

TLM is conducted according to the principles proposed by Wolfgang Steiner and Petra Ambrosch.[96]

As per the standard technique, tumours are removed in several (at least two) planned pieces following transtumoral resection. Transtumoral resection is necessary for two primary reasons: primarily, it eases the technical burdens of removing large tumours which is of particular importance when resection is taking place down a distending endoscope as is usual when resecting tumours of the BOT. In addition, it facilitates greater appreciation of the 3D orientation of the tumour allowing greater resection precision. In an attempt to confirm complete surgical removal representative marginal biopsies should be taken from the tumour bed and examined histologically.

Marginal biopsies should be taken from all peripheral mucosal regions when this is technically feasible, together with representative marginal deep biopsies from the tumour bed.

The technique of TLM resection for OPSCC is best described when considering resection of a primary tonsil tumour.

Most tonsil tumours considered amenable to TLM are T2 in size. Resection will typically involve removal in two parts, following an initial transverse laser cut through the centre of the tumour which divides it into superior (cranial) and inferior (caudal) halves. Thereafter, each half is removed separately. Following in continuity removal of a given half, it is usually orientated and pinned to a cork board. On removal of the other half, this too is orientated and pinned to the same cork board, to recreate the anatomical arrangement of the primary tumour.

It is from this pinned primary specimen that histological margins around the primary tumour will be determined.

Having removed the two halves of the primary tumour, marginal biopsies are then taken. Marginal biopsies, as far as anatomically possible, should maximally represent the mucosal regions adjacent to the primary tumour and the deep tumour bed (**Figure 13.12**). It is usual therefore to take up to eight marginal biopsies following a standard TLM of a tonsil tumour, namely:

- a superior marginal biopsy involving the mucosa adjacent to the superior pole of the tumour
- an anterosuperior marginal biopsy, from the mucosa anterior to the superior half of the tumour (in many cases this amounts to the mucosa covering the region of the anterior faucial pillar)
- a posterosuperior marginal biopsy, from the mucosa posterior to the superior half of the tumour (in many cases this amounts to the mucosa covering the region of the posterior pharyngeal wall)
- a superior deep marginal biopsy which includes a representative sample of constrictor muscle deep in the bed of the superior half of the tumour
- an inferior marginal biopsy involving the mucosa adjacent to the inferior pole of the tumour
- an anteroinferior marginal biopsy, from the mucosa anterior to the inferior half of the tumour (in many

Figure 13.12 A tonsillar carcinoma, resceted in two portions as per the TLM principles described by Steiner and Ambrosch. Each section is anatomically re-orientated and pinned to a cork board (orange needles). A mucosal marginal biopsy is also anatomically orientated adjacent to the superior edge of the superior specimen. The superior pole of the tonsil is marked with a blue needle.

cases this again amounts to the mucosa covering the region of the anterior faucial pillar)
- a posteroinferior marginal biopsy, from the mucosa posterior to the inferior half of the tumour (in many cases this too amounts to the mucosa covering the region of the posterior pharyngeal wall)
- an inferior deep marginal biopsy which includes a representative sample of constrictor muscle deep in the bed of the inferior half of the tumour.

The biopsies should be labelled as above prior to sending to the pathology laboratory. The taking of marginal biopsies around soft palate and BOT tumours is more difficult to mandate as, in keeping with the philosophy of TLM, to tailor the resection to the tumour extent, there is often no standard procedure for removing these tumours. However, the guiding principles of marginal biopsies – to maximally represent adjacent mucosal boundaries and the deep tumour bed of resected tumours – should be adhered to at all times.

If all marginal biopsies are free of microscopic disease, then resection of the primary tumour is considered to be complete and allocation of adjuvant treatment depends, *inter alia*, on the depth of the resection margin around the main tumour specimen(s).

Re-resection is usually undertaken in a case when one or more initial marginal biopsies are found to contain microscopic disease.

Transoral robotic surgery (TORS)

(For more information regarding the role of TORS in general, please see Chapter 80, Rhinoplasty following nasal trauma)

For tonsil and BOT tumours, it is usual for the neck dissection be performed prior to the TORS procedure, either during the same general anaesthetic or at a previous sitting, during which the ipsilateral lingual and facial arteries are identified and ligated in continuity.

The resection involves *en bloc* removal of the tumour as per the principles outlined in the da Vinci Transoral Surgery Procedure Guide, which can be accessed via the following link.[97] https://oto.med.upenn.edu/education/62-2/.

The resection is performed primarily with the monopolar cautery. Where facilities are available to couple a laser to the robotic arm, this may be used for the resection.

Tonsil tumours: Resectability of the tonsil tumour is confirmed based on imaging. Extension to the parapharyngeal space and pterygoid musculature are relative contraindications to the procedure. Retropharyngeal location of the internal carotid artery is also a contraindication for this procedure and the scans should be very carefully studied to ensure this is not the case. The resection specimen is essentially a lateral oropharyngectomy, where the constrictor muscles of the tonsil bed are removed along with the tumour. If any concerns arise regarding the adequacy of the margins during the resection, the margins can be extended. Following removal, the tumour is grossly inspected to ensure that adequate margins are obtained. This may involve cutting though the tumour with a blade if the expertise and facilities exist. If any concerns are raised about the margins following resection (this usually occurs at the inferior aspect, where the tonsil meets the tongue base), the areas are marked with methylene blue (to identify the surface of interest to the pathologist) and a further margin harvested. The specimen is orientated on a suitable mount and sent for histological examination.

Tongue base tumours: Resectability of the tongue base tumour is also confirmed on imaging. Tumour extending across the midline is a contraindication for the procedure. Resection of the ipsilateral tongue base is performed as described in the procedure guide above. If any concerns are raised about the margins following resection (this usually occurs at the deeper aspect of the BOT), the areas are marked with methylene blue (to identify the surface of interest to the pathologist) and a further margin harvested. The specimen is orientated on a suitable mount and sent for histological examination.

Tumours involving both the tonsil and BOT: These tumours usually do not involve the entire tonsil and thus, it is sufficient to cut through the tonsil and the constrictors at least 5 mm away from the tumour edge and proceed with the resection of the tonsil tumour in the usual fashion, leaving the cranial part of the tonsil. Once the tonsil tumour is completely mobilized down to the styloglossus, the tongue base cuts can be made and the entire tumour removed *en bloc*. As above, further margins are resected on the table if concerns exist. The specimen is orientated on a suitable mount and sent for histological examination.

As outlined above, in contrast to the principle of TLM, primary tumours are removed *en bloc* using TORS in the vast majority of cases. As a result, surgical margins after TORS can be assessed and measured using standard pathology reporting protocols and the taking of marginal biopsies does not apply to tumours resected in this way. However, transtumoral resection and the taking of marginal biopsies – as described for TLM - may also be appropriate when employing a TORS approach and in such cases the same criteria for assessing resection as outlined for TLM above, should be employed.

In the specific instance that *en bloc* resection has been attempted but histological examination confirms a positive (involved) resection margin or margins, the following recommendations apply.

- If the positive margin(s) is mucosal then further resection to confirm complete excision is permitted. In this case, risk group allocation will rely on the histological status of the re-resected mucosal margin(s).
- If the positive margin is deep, then in keeping with the principles of TORS, re-resection is not recommended due to the anatomical limitations of undertaking further resection lateral to the constrictor muscles or deep to the prevertebral fascia. In such cases, patients will automatically be categorized as pathologically high risk.

A retrospective US study of 204 patients with stage III-IV OPC treated with primary TLM and neck dissection reported 3-year rates of local control, overall survival and disease-free survival of 97%, 86% and 82% respectively,

which were higher in HPV+patients.[59] A retrospective series from Liverpool, UK of 153 patients with T1-T3 OPSCC (66% were HPV+) treated with TLM and neck dissection, reported 3-year rates of disease-specific survival, overall survival and disease-free survival of 91.7%, 84.5% and 78.2% respectively, again better in patients with HPV+ disease.[60]

Similarly good outcomes have been reported following TORS: a cohort study of 410 patients from 11 centres treated with TORS, +/- adjuvant RT/CRT, reported 2-year rates of locoregional control, disease-specific survival and overall survival of 91.8% (95% CI, 87.6–94.7%), 94.5% (95% CI, 90.6–96.8%) and 91% (95% CI, 86.5–94.0%) respectively.[98]

No randomized studies have yet compared outcomes following transoral surgery and RT/CRT for OPSCC. Nevertheless, a recent meta-analysis on early stage OPSCC reported comparable 5-year disease-specific survival rates of 90.4% (95% CI, 85.6–95.2%) for RT and 89.6% (95% CI, 81.8–97.3%) for TOS in early stage OPSCC.[27] Furthermore, a systematic review comparing the effectiveness of IMRT and TORS for T1-T2 OPSCC[28] reported similar survival outcomes in 1287 IMRT patients (2-year overall survival 84–96%) and 702 TORS patients (2-year overall survival 82–94%). A different profile of adverse events were reported for IMRT and TORS, which for IMRT included gastrostomy tubes (43%), oesophageal stenosis (4.8%) and osteoradionecrosis (2.6%) and for TORS as described below.

Transoral surgery for early and intermediate stage OPSCC is generally well tolerated, with a median length of hospital stay after surgery of approximately 4.4 days.[59] Acute complications include haemorrhage (2.4%) and fistula (2.5%). Temporary tracheostomy tubes are needed in 12% of patients at the time of surgery but most are decannulated prior to discharge.[99] Temporary nasogastric tubes are required in up to 47% of patients post-operatively but most patients can manage an oral diet without a tube by 4 weeks following surgery.[100, 101] Long-term functional outcomes after TOS appear favourable in small studies: in a study of 30 patients with early (mainly T1-2 N0-N1) OPSCC treated with TORS and neck dissection (without adjuvant treatment), all patients were taking a full oral diet without a feeding tube after a median follow-up of 2.7 years.[62]

However, in most reported series of TOS, the majority of patients also undergo adjuvant therapy, either with post-operative RT (PORT, 21–58% of cases) or post-operative CRT (POCRT, 16–62% of cases.[60, 61, 101–103] It is clear that adjuvant treatment increases acute and late toxicity associated with transoral surgery. In the largest TLM series,[60] adjuvant treatment doubled gastrostomy tube use from 17% to 33% and 19% of patients remained gastrostomy tube dependent 12 months after treatment. In 66 OPSCC patients treated with TORS,[101] 97% were tube free and managing an oral diet 4 weeks after surgery, but 27% (18/66) required a gastrostomy tube during their adjuvant therapy and 3 (4.5%) remained gastrostomy tube dependent more than 2 years after treatment. In 81 patients treated with TORS,[104] all patients were discharged post-operatively on full oral diet, but 13 (16%) required gastrostomy tube placement during adjuvant treatment; of these, five remained in place for over a year. Eating domain health related quality of life (HRQOL) scores were also significantly worse in patients who underwent adjuvant treatment compared to those who did not. Increasing age (>55 years) and extent of TORS resection predicted the need for a gastrostomy tube and high T stage (pT3/pT4) predicted the need for permanent tube feeding. Not surprisingly, functional outcomes following POCRT appear to be worse than after PORT. In 38 OPSCC patients, speech, diet and eating (PSS-H&N) scores at 6 and 12 months following treatment were significantly better following TORS alone compared to TORS followed by PORT which were, in turn, better than after TORS and POCRT.[105] Furthermore, a systematic review of TORS for OPSCC showed clear demarcation in swallowing outcomes across a variety of outcome measures in patients who received PORT compared to POCRT.[106]

It is clear that current adjuvant treatment protocols limit the use of TOS as a potential means of improving long-term function, whilst maintaining good oncological outcomes, in patients with OPSCC. This issue has been raised in particular in the context of HPV+OPSCC. However, adjuvant treatment decisions are based on pathological risk factors for recurrence established >20 years ago in studies which included a heterogeneous group of HNSCCs, most of which were treated with open (not transoral) surgery and none of which were tested for HPV[107, 108] and their relevance to the selection of adjuvant therapy regimens and doses in the context of HPV-positive disease have been questioned. A National Cancer Institute Head and Neck Cancer Steering Committee Clinical Trials Planning Meeting on transoral resection of pharyngeal cancer called for these parameters to be re-evaluated for HPV+ disease in controlled, prospective surgical trials with clinical-pathological correlation of outcomes.[109] US and UK clinical trials, ECOG 3311 and PATHOS (described in more detail later), are currently recruiting in an attempt to address this lack of data.

Management of the neck

The role of the neck dissection in the treatment of oropharyngeal cancer is well standardized and outlined in detail in the UK Head and Neck Cancer Multidisciplinary Management Guidelines 2016.[52]

CLINICALLY NO NECK

The prevalence of micrometastatic nodal disease in OPSCC patients presenting without clinical or radiological evidence of nodal disease is estimated to be between 10% and 30% accordingly, in most cases, elective treatment of the neck is recommended. Surgery, in the form of a selective neck dissection or radiotherapy, is a valid option. Which is chosen is typically predicated on the choice of treatment used for the primary tumour as the aim in early stage disease is for single modality treatment.

NECK DISSECTION

In patients with a lateralized tumour – see 'Radiotherapy planning' above for definition – an ipsilateral neck dissection suffices.

In patients with a non-lateralized tumour – see 'Radiotherapy planning' above for definition – then the contralateral neck should also be dissected if only for pathological staging purposes.

A selective neck dissection including the dissection of, at least, lymph node levels II and III and possibly level IV should be performed. There is also some evidence to recommend the dissection of level I in the case of anterior disease extension.[110] There is no evidence which mandates the dissection of level IIB in the context of clinically N0 disease.

Particularly when TORS is used for primary tumour resection, as described above, it is common for the neck dissection to be carried out as a staged procedure some 2 weeks prior to the primary resection. This is primarily recommended as a strategy to reduce the rate of pharyngocutaneous fistula (PCF) although in practice a staged approach is often dictated by local logistics relating to robot availability. The opportunity is taken, during the neck dissection, to ligate the branches of the external carotid artery which supply the lateral oropharynx (ascending pharyngeal, lingual and facial arteries). This is performed to reduce the local blood pressure with the aim of reducing major haemorrhage following primary tumour resection.

In contrast, when TLM is used for primary tumour resection, it is usual to perform the neck dissection, including the ligation of the external carotid artery branches, during the same anaesthetic. Which is performed first is a matter of personal choice. The risk of PCF is extremely small, especially if lymph node level I is not dissected. It the case where a PCF does occur, repair using local tissues such as the digastric or sternomastoid muscle, followed by a 5-day period of nasogastric feeding, is usually sufficient to allow successful PCF healing.

Although the goal for the treatment of early stage disease is single modality treatment, pathological findings (close or involved surgical margins, pN+ disease +/- ECS) following surgical resection may mandate the need for adjuvant RT +/- chemotherapy. It is for this reason there has been resistance to the use of surgery (to the neck and primary site) for the treatment of OPSCC, particularly in the HPV era. If adjuvant RT is required it should be planned according to the principles used for radical RT (see 'Radiotherapy' below), but a reduced dose of 60 Gy in 30 fractions is usually recommended.

RADIOTHERAPY

Prophylactic radiotherapy should be given to the ipsilateral cervical lymph nodes for lateralized (e.g. tonsillar) tumours and to both sides of the neck for non-lateralized tumours (see 'Radiotherapy planning' above). Radiotherapy to levels II/III/IVa is recommended; level Ib may also be included in cases with anterior extension of tumour and/or involvement of the anterior tonsillar pillar. Neck node levels should be outlined according to the DAHANCA, EORTC, HKNPCSG, NCIC CTG, NCRI, RTOG, TROG consensus guidelines and the associated on-line atlas.[76]

Treatment of the node positive neck

NECK DISSECTION

If the neck is considered operable and surgery is the primary treatment modality then an N+ neck should be treated by selective neck dissection including, at least, levels IIA, III and possibly IV. Additional nodal levels may be dissected as indicated by the volume and level of apparently involved lymph nodes. It is usual to dissect level IIb in the N+ neck and again, level I may be dissected in some instances where anterior extension of the primary tumour is marked. Whether, or which, adjuvant treatment – RT +/– chemotherapy – is required will be dictated by the surgical pathology although avoidance of adjuvant treatment, at least to the primary site, is highly unlikely in the context of T3 or T4 disease.

RADIOTHERAPY/CHEMORADIOTHERAPY (CRT)

The principles of radiotherapy outlining and planning are as described for earlier stage disease. Neck nodes should be included in the treatment fields depending on their probability of involvement and according to the DAHANCA, EORTC, HKNPCSG, NCIC CTG, NCRI, RTOG, TROG consensus guidelines and atlas which were updated in 2013.[77, 111] Radiotherapy to levels Ib–IVa, V(a,b) and the retropharyngeal nodes (level VIIa) at the level of the oropharynx is generally recommended in a N+ neck. The retrostyloid space (level VIIb) is included when level II is involved and the SCF (level IVb and level Vc) is included when level IVa or V are involved. The nodal levels to be included are summarized in **Table 13.1.** Radiotherapy should be given to at least the ipsilateral cervical lymph nodes for lateralized tumours and to both sides of the neck for non-lateralized tumours. The issue of whether the contralateral neck should be treated in patients with lateralized oropharyngeal tumours and advanced (N2+) nodal disease remains controversial and will depend on local practice.[111]

A recently reported phase III RCT that patients with N+ OPSCC can be effectively treated with CRT, without the need in most cases for a neck dissection. The PET NECK trial[112] confirmed that a post-treatment PET-CT surveillance policy, with neck dissection only being performed for patients who have FDG positive or equivocal residual nodal disease on PET-CT scanning at 12 weeks after completion of CRT, results in equivalent survival and regional control rates compared to a planned neck dissection, with a significant reduction in morbidity (by avoidance of surgery in 4 out of 5 patients) and improved cost effectiveness.

TREATMENT FAILURE

The landmark study by Ang et al,[7] which retrospectively considered outcomes of patients with stage III/IV OPSCC, treated with one of two CRT regimes and for whom HPV status had been established confirmed the improved survival outcomes seen for patients presenting

with HPV+OPSCC compared with patients presenting with HPV-OPSCC. The follow-up data also confirmed that significantly more patients in the HPV-OPSCC group had relapsed locoregionally than those in the HPV+OPSCC group (35.1% (95% CI, 26.4–43.8%) vs 13.6% (95% CI, 8.9–18.3%)), although the rate of distant metastasis did not differ significantly between the groups. Patients with HPV-OPSCC and a subset of patients with HPV+OPSCC also have less favourable outcomes in studies where patients were managed with primary surgery.[60, 61]

A retrospective cohort analysis of 185 patients with OPSCC treated with RT and cisplatin +/– tiranzapine by Rischin et al[113] also confirmed that locoregional recurrence was more likely in the HPV- group (14% vs 7%) although the rates of distant relapse were similar in each group.

Similar data were published by Posner et al[114] in a study of 111 patients with local advanced OPSCC. They, too, confirmed an increased rate of locoregional relapse in patients with HPV- tumours at 5 years compared with HPV+patients with similar rates in distant relapse in each group.

Huang et al,[115] in a study which included 624 OPSCC patients similarly concluded that locoregional relapse was statistically more likely in patients with p16- disease compared to those with p16+ disease (21% vs 6%), whilst distant relapse rates were similar.

Collectively these data confirm that locoregional relapse, in contrast to distant relapse, is statistically more likely in patients with HPV+OPSCC, but that the rate of relapse (locoregional and distant) in the HPV+ group is not insignificant and represents a subgroup of patients with HPV+ disease who do badly.

Although the rates of distant relapse appear similar between HPV+ and HPV- patient groups, other data[116, 117] reporting on the pattern of post-treatment distant metastatic spread at relapse in patients with OPSCC confirm obvious differences between HPV+ and HPV- groups.

Whilst the most common pattern of distant spread to the lung, bone and liver is similar between the groups, a subgroup (~30%) of patients with HPV disease develop metastases at unexpected anatomical sites including brain, skin and intra-abdominal lymph nodes. Moreover, it appears that these atypical patterns of spread are harbingers of aggressive tumour behaviour with patients experiencing rapid deterioration following diagnosis.

Despite this subgroup of patients with atypical spread which do extremely badly, overall patients with HPV+OPSCC still fare better after relapse than patients with HPV- disease although the magnitude of beneficial impact in the relapse setting is much smaller than the effect of HPV positivity in the primary disease setting.[115, 116, 118, 119]

Currently, predictive biomarkers of outcome are not available and so identification of the subgroup of HPV+patients destined for poor outcome is currently not possible. Furthermore, as things stand, it is unclear how best to treat patients at relapse and additional high-quality clinical trials designed to address this need are urgently needed.

THE FUTURE

Optimizing treatment for OPSCC: ongoing clinical trials

As explained previously, the emergence of HPV+OPSCC as a discrete disease entity has resulted in the need to identify novel de-intensified treatments for HPV+OPSCC which will maintain the current advantageous survival outcomes whilst reducing the acute and long-term adverse effects of current treatments. In contrast, the quest to identify tolerable intensified treatments for patients with HPV-OPSCC in an attempt to improve current modest survival outcomes, is ongoing. Moreover, there still remains an absence of level I evidence comparing surgical vs non-surgical treatment strategies.

Ongoing clinical trials are attempting to address these voids in our current clinical knowledge.

An EORTC phase III randomized study (EORTC 1420, 'Best-Of' NCT02984410) comparing late function (MDADI at 12 months following treatment) after TOS and IMRT in patients with (HPV+ and HPV-) T1-T2 N0 M0 OPSCC is currently recruiting in several European countries, including the UK and could inform future practice for early stage disease by providing much needed level I evidence following a head-to-head comparison of surgical vs non-surgical treatment.

Similarly, the currently recruiting Canadian ORATOR phase II clinical trial (NCT01590355) will attempt to address the same problem.

Patients with T3-4 OPSCCs, which are not transorally resectable, should undergo primary CRT as the standard of care. Dysphagia optimized IMRT, aiming to minimize radiation dose delivery to swallowing-related structures, and/or the use of cetuximab instead of cisplatin with RT, are being studied in ongoing UK clinical trials (DARS, ISRCTN: 25458988 and De-ESCALaTE-HPV, NCT01874171 respectively), as means of reducing toxicities in these patients.

In addition, The Quarterback Trial (NCT01706939): A Randomized Phase III Clinical Trial Comparing Reduced and Standard Radiation Therapy Doses for Locally Advanced HPV Positive Oropharynx Cancer, has completed recruitment and is in follow-up.

As an alternative approach, the UK phase II/III PATHOS study (ClinicalTrials.gov NCT02215265) (40), and the US study ECOG 3311 [NCT01898494]) are currently exploring transoral surgery (TLM or TORS) +/– de-intensified adjuvant as a potential means of improving long-term function, whilst maintaining good oncological outcomes, in patients with HPV+OPSCC.

PATHOS[120] (see **Figure 13.13** for trial schema) is currently recruiting patients with HPV+OPSCC who will undergo transoral surgery and a neck dissection. Post-surgical pathology will allow stratification into three distinct risk

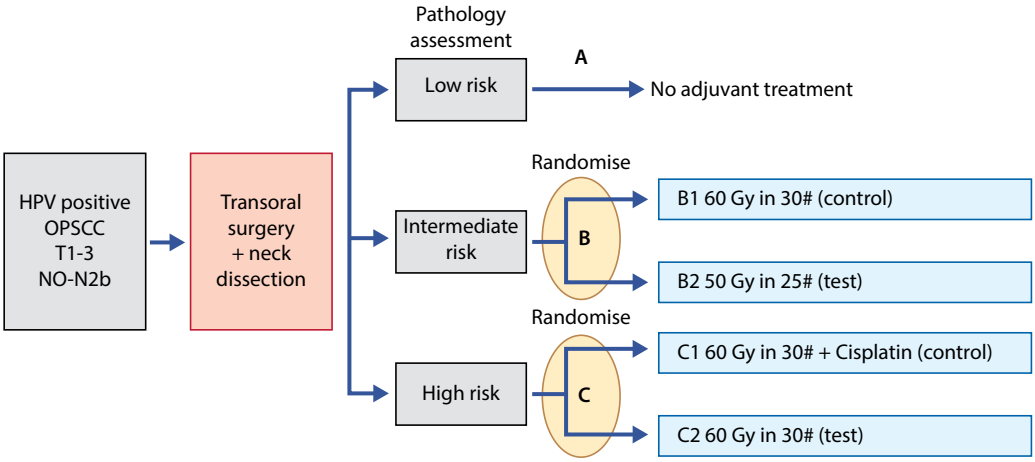

Figure 13.13 PATHOS (Post-operative adjuvant treatment for HPV+OPSCC study schema. Patients with T1-2 N0-N2b HPV+OPSCC undergo transoral surgery and a neck dissection before being stratified into groups (A, B and C) based on pathological risk factors. Group A (no risk factors) have no adjuvant treatment. Group B (N2, close margins, perineural /vascular invasion) are randomized to 60 Gy (control arm) or 50 Gy (test arm) of IMRT. Group C (ECS and/or high risk margins) are randomized to POCRT (control arm) or 60 Gy PORT only (test arm). Primary endpoint, Overall survival; Secondary endpoint, swallowing function, as measured by a multi-instrument swallowing panel, at 1 year post-treatment.

groups. Whilst a low-risk Group A will receive no adjuvant treatment an intermediate risk Group B will be randomized between standard and reduced dose adjuvant IMRT and a high-risk Group C will be randomized between adjuvant CRT and standard dose IMRT alone. A European phase III extension to the ongoing UK phase II is planned to investigate whether de-intensified adjuvant treatment schedules for patients with intermediate stage HPV+OPSCC, undergoing transoral surgery, results in non-inferior survival outcomes and improved swallowing function.

In contrast, poor prognosis OPSCC, including HPV+ current smokers[22] with advanced disease and patients with HPV-disease, may benefit from treatment intensification and an ongoing multi-arm, multi-stage (MAMS) UK study (COMPARE, UKCRN Study No: 18621) is exploring this possibility.

Translational research

What is clear is that many questions relating to the epidemiology and natural history of oral HPV infection and its relationship to the development of HPV+OPSCC remain. Some of the more pressing questions which are currently the basis of ongoing research include:

- Why do a small percentage of infected individuals fail to clear the initial HPV infection and why do a proportion of these then go on to develop HPV+OPSCC?
- Is the mechanism of infection and virally mediated transformation the same for OPSCC as for cervical cancer and why is HPV-16 the predominant genotype involved in OPSCC whilst HPV-18, together with HPV-16, has a more significant role in the development of cervical cancer?
- Why is OPSCC more responsive to treatment than cervical cancer despite presenting with clinicopathological features traditionally associated with poor outcome?
- Does an as yet undetected HPV+OPSCC premalignant lesion exist?
- Why is there a significant male:female gender bias?
- Why has this new discrete disease entity only emerged in the last 3–4 decades?

Moreover, there is an urgent need to identify robust predictive risk-stratifying biomarkers which will identify the subgroup of patients with HPV+ disease. The identification of such biomarkers is planned as a translational programme of research allied to several of the clinical trials highlighted above e.g. RTOG 1420, PATHOS, De-Escalate and COMPARE.

Following on from this, there is also an urgent need to identify novel treatments which will reduce rates of treatment failure and/or enhance life-expectancy in patients who relapse.

Of particular note in this context is the publication of the CheckMate 141 clinical trial.[121] This randomized, open-label, phase III clinical trial, randomized 361 patients with recurrent SCCHN, whose disease had progressed within 6 months of receiving platinum based CRT in a 2:1 ratio to receive nivolumab or standard single-agent systemic therapy. The primary end-point was overall survival. Overall survival was significantly longer in the group that received nivolumab compared with the group treated with standard systemic therapy (7.5 months vs 5.1 months: HR for death = 0.70; 97.7% CI 0.51–0.96%). A post-hoc exploratory analysis of 178 patients with OPSCC for whom p16 status was known confirmed that among the patients with p16+ tumours OS was 9.1 months in the nivolumab group vs. 4.4 months in the standard therapy group (HR for death = 0.56; 95% CI 0.32–0.99%), suggesting that PD-1 blockade may have a discriminatory advantage in patients with HPV+OPSCC in the recurrent / metastatic setting.

Prophylactic vaccination

Vaccination of girls against HPV has been implemented in many countries throughout the developed world with the aim of protecting women against cervical cancer. Gender-neutral vaccination for boys, with the aim of preventing HPV related cancers to which males are exposed, anal, oropharynx and penile, is more contentious. Currently, only the United States, Austria, Canada and Australia recommend vaccination for boys but only Australia has implemented a comprehensive nationwide vaccination programme for boys aged 12–13 years.

The main reason against widespread introduction of gender neutral vaccination is cost-effectiveness. Assessing cost-effectiveness is a relatively complex process as underpinning the successful protection of males is the effectiveness of herd-immunity which is predicated on vaccine take-up in girls. Modelling data confirm that if vaccine coverage in women exceeds 80% then herd-immunity will be sufficient to ensure the protection of males. This argument, however, is based on two main assumptions.

- A high level of vaccine coverage is uniform and sustainable in the long term across the whole female population being vaccinated.
- Males only have sex with vaccinated females.

If each of these assumptions are correct, then population-based vaccination of boys is arguably not cost-effective. Campaigners for the introduction of gender-neutral vaccines propose the following counter arguments:

- That uniform and sustainable vaccination of girls in any given country cannot be guaranteed and that there are areas and populations in all countries – London and certain ethnic and religious groups in the UK for example – where vaccination rates will be far less than 80% so that herd immunity is not guaranteed.
- In an increasingly globalized world men will not only have sex with women from countries where comprehensive vaccination programmes are in place and neither does this assumption take into account the men who have sex with men (MSM) – a group at particularly high risk of developing HPV-related cancers.
- Cancer inequalities will be augmented as males from more affluent backgrounds will be vaccinated privately.
- That choosing to vaccinate only one gender when it is known that the non-vaccinated gender is at risk of harm, albeit not to the same extent, is discriminatory.

Debates such as these are playing out in most developed countries in the world and certainly the proponents for gender neutral vaccination now have the support of high-profile scientific and medical opinion leaders.

Whatever the outcome, it is clear that any positive effect of prophylactic vaccination on the incidence of HPV+OPSCC is likely to be delayed for several decades and in the intervening time it is incumbent upon all involved to continue to strive to improve the outcomes for the patients unfortunate enough to develop this devastating condition.

KEY POINTS

- Globally, the incidence of oropharynx cancer is increasing rapidly in a geographically variable pattern.
- Most of this increase is attributable to a rise in Human papillomavirus related disease (HPV+) although non-HPV related disease (HPV-) appears also to be increasing in some countries.
- HPV+ oropharynx cancer (HPV+OPSCC), constitutes a discrete disease entity, presenting in patents who are younger, fitter and more affluent than patients presenting with HPV- disease.
- Despite presenting with clinicopathological features (N+ with ECS) usually associated with poor disease outcome, HPV+ tumours respond better to treatment.
- In light of this, attention has turned to the potential for de-intensified treatment strategies for HPV+OPSCC, in order to maintain advantageous survival outcomes whilst reducing treatment-related early and long-term toxicity.
- Despite a widespread perception that HPV+OPSCC is a defined sexually transmitted disease, this has yet to be confirmed.

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CHAPTER 14

TUMOURS OF THE LARYNX

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SEARCH STRATEGY

The data in this chapter are based on searches of Medline, EMBASE and the Cochrane Library using the keywords: laryngeal cancer, squamous cell cancer, laryngeal dysplasia, diagnosis, treatment. The articles referenced by these authors were also reviewed. The data are supplemented by further searches of specialized books.

INTRODUCTION

Laryngeal carcinoma is the most common site of malignancy in the head and neck worldwide. The effects of the disease process and the treatment can have significant impact on voice and swallow function and quality of life. Recent advances in the surgical and non-surgical management options, with a burgeoning evidence base, have led to a sea change in the management of laryngeal cancer in the last decade. This chapter will deal with the principles of assessment, diagnosis and management of laryngeal precancer and cancer. The finer aspects of endoscopic, open and robotic surgery for laryngeal cancer merit detailed treatment and are dealt with elsewhere in the book.

EPIDEMIOLOGY

Worldwide, laryngeal tumours account for 156 000 new cases per year and 83 000 deaths. The incidence is higher in men worldwide, with an estimated 138 000 men being diagnosed each year compared to 18 000 women. There are significant variations in incidence across the world.[1] Laryngeal tumours are most common after the age of 60 and less common under 40.[2]

In the UK, the age standardized incidence of laryngeal cancer is estimated to be 3/100 000. Within the UK there are wide variations in incidence with the highest incidence in the north of the country. Overall, the incidence of laryngeal cancer has decreased by 20% since 1990 and appears to have plateaued between 2002 and 2006. This has largely been attributed to a reduced incidence of smoking. Yet other factors such as changes in the industrial landscape and decline in heavy industry could also have contributed. Concurrent with a drop in incidence, the survival following a diagnosis of laryngeal cancer has continued to improve in the UK; between 2002 and 2006 the figures improved from 82.75% to 85.33%. However, the 5-year relative survival rates have remained unchanged over the same period at 65% for the most recently diagnosed cases.[3]

Data from the United States also suggest that there are significant variations in incidence between racial groups, with the majority of tumours occurring in Caucasian patients.[4] A detailed treatment of epidemiology can be found in Chapter 3, Epidemiology of head and neck squamous cell carcinoma.

AETIOLOGY

Smoking remains the most common aetiological factor for cancers of the larynx, with alcohol an independent risk factor for developing laryngeal cancer in the absence

of smoking. The combination of smoking and alcohol appears to be a multiplicative risk.[5] The risk of developing laryngeal cancer is highest in current smokers and increases with the number of cigarettes smoked. There is a reduction in relative risk of developing laryngeal cancer after stopping smoking and drinking with the risk reduction reaching the level of never smokers after approximately 20 years.[5, 6]

While sexual behaviours and HPV infection have been strongly linked with tumours of the oropharynx, there is little epidemiological evidence linking these with tumours of the larynx.[7, 8] Unlike oropharyngeal cancer, existing retrospective studies do not identify a favourable prognostic impact for HPV positive laryngeal tumours.[9, 10]

Other known risk factors include occupational toxic agents such as asbestos, polycyclic aromatic hydrocarbons, wood dust, coal dust and cement dust.[11, 12] Lower socioeconomic status and manual 'blue-collar' occupations also experience a higher risk of developing laryngeal cancer.[11]

Certain genetic syndromes, such as Fanconi anaemia[13] and congenital dyskeratosis[14] are also associated with a higher risk of developing laryngeal tumours in addition to tumours in other parts of the body. A detailed treatment of aetiology of laryngeal cancer can be found in Chapter 2, Aetiology of head and neck cancer.

PATHOLOGY

The most common type of laryngeal cancer is squamous cell carcinoma; however, many other histological types of cancers can be seen in the larynx. A detailed discussion of the various pathological entities in the larynx can be found in Chapter 26, Head and neck pathology.

Optimal pathological assessment of specimens requires a co-ordinated approach between the pathologist and surgeon or oncologist. The Royal College of Pathologists in the UK have published guidelines for the dataset required to report cases. Important factors including the type, size and grade of the primary carcinoma, the pattern of invasion and proximity of carcinoma to resection margins. All have been shown to be important prognostic features.[15] It is crucial that small specimens resected via transoral approaches are oriented prior to pathological analysis to allow accurate reporting of the margins. Several options exist for mounting specimens, which is discussed in detail in 'Transoral laser microsurgery' below. To maintain clear lines of communication, the authors' preference is to send pictures of the resected, mounted specimen, which is then marked, to the pathology team. In cases where a total or partial laryngectomy has been performed, whole organ section analysis is usually performed to consider patterns of spread and resection margins. HPV testing is not considered routine but may be important in a subset of patients.

PATHWAYS OF CANCER SPREAD

Laryngeal squamous cell carcinoma has characteristic patterns of spread depending on the site of origin. Local spread is along tissue planes, while lymphatic spread is guided initially by the boundaries between embryological anlagen (arches III–VI), notably at the free edge of the glottis. Yet, despite long-held beliefs, there is no true anatomical barrier to check spread between the supra- and subglottis, as was shown as long ago as 1969 by Kirchner's laborious whole organ dissections.[16]

Historically, glottic cancer spreading to the anterior commissure (AC) was feared, because early invasion through Broyle's ligament directly into cartilage was thought inevitable. This was perceived to be due to the lack of an inner perichondrium in that area. However, recent work has shown that the ligament is in fact an effective barrier, but it is extension superiorly and inferiorly (via subglottic wedge and hence cricothyroid membrane) that worsens prognosis. Direct spread may continue via the AC to the opposite cord, or may extend posteriorly to invade the arytenoid cartilage. Glottic tumours may be confined to Reinke's space by the embryological boundary superiorly and the conus elasticus inferiorly. To reach the paraglottic space and thence gain an easy passage cranially and caudally, tumours need to transgress both the vocal ligament and vocalis muscle. The laryngeal skeleton is relatively resistant to invasion, though ossified areas appear less so. Nonetheless, external extension directly through the cartilages is regularly seen.

Lymphatic spread of glottic cancer is less common than at other subsites. It has been suggested that the lack of submucosal lymphatics in this area is responsible. However, detailed studies of mucosal cell trafficking have not yet been performed to confirm this. Spread, when it occurs, is to levels II, III, IV and VI. Estimates for the incidence of macroscopic lymph node metastasis by disease stage are: <5% (T1), 7% (T2), 14% (T3) and 33% (T4). The so-called 'Delphian' node (also known as the midline anterior metastatic node or Poirier's pre-laryngeal ganglia node) is very rare, but is thought to be associated with T3 or T4 tumours with significant subglottic extension.

Supraglottic cancers tend to remain locally confined (even with pre-epiglottic or nodal spread) to their subsite until relatively late. As a result, supraglottic laryngectomy is often a viable option even for bulky tumours. However, as noted above, there is no real anatomical barrier to inferior spread. Indeed, the routine use of angled Hopkins rods during staging procedures to examine the cavity of the laryngeal ventricle reveals a steady transmucosal progression of tumours similar to other subsites and permits the precise selection of patients suitable for supraglottic partial laryngectomy. Overall, several studies have shown that approximately 50% of supraglottic cancers spread to the glottic region. The presence of foramina within the epiglottic cartilage makes this less of a barrier to spread than that presented by the other cartilages. However, invasion of the hyoid is rare (2–4%), meaning that it can often be retained during operative clearance. 'Suprahyoid supraglottic' carcinomas tend to invade the pre-epiglottic space and the deep muscles of the tongue and spread mucosally into the piriform fossae rather than into the paraglottic space. Supraglottic tumours also have a propensity for bilateral nodal metastasis. In reports of

advanced disease, supraglottic carcinoma has a positive nodal rate of over 60%, compared with much lower rates of 20% in advanced glottic cases. This has a major influence on the decision to perform elective neck dissections for these patients (see Chapter 36, Clinical examination of the neck).

Subglottic carcinoma tends to extend caudally and circumferentially. Fifty percent invade the cricoid and 75% have already extended outside the larynx by the time of diagnosis. Despite this, clinically detectable nodal metastasis is surprisingly uncommon, although a microscopic incidence of one in three puts this disease into the category of requiring elective nodal dissection. Due to the propensity for inferior extension, nodal dissection for subglottic cancer should include the paratracheal/mediastinal nodes.

Transglottic cancer is defined by spread, both superficially and into the paraglottic space to span all three laryngeal subsites. True primary transglottic cancer is said to originate in the laryngeal ventricle, though in practice it is impossible to be precise about the original epicentre. It is, by definition, at least T3 at presentation and subsequent consideration will therefore be alongside advanced cancers.

Tracheal squamous cell carcinoma is exceedingly rare, with approximately eight cases per annum in the UK and one in Holland, despite being theoretically exposed to the same carcinogens as the larynx. Interestingly, the trachea has the highest density of immunologically active cells suggesting that mucosal immunosurveillance may be a crucial factor in defence against airway mutagenesis. A rule of thumb for spread in each site is given in **Table 14.1**.

Thyroid gland invasion has been studied in resected specimens and the incidence of this has been studied in a systematic review by Kumar et al.[17] Pooling data from 1287 patients, this study showed that the overall incidence of thyroid gland invasion is 10.7% (95% CI 7.6–14.2). Patients with primary subglottic tumours (relative risk 7.5; 95% CI 4.3–13.0) and disease extension into the subglottis (relative risk 4.3; 95% CI 2.5–7.2) have a significantly higher relative risk of thyroid gland invasion. Other sites did not confer this higher risk. As the overall incidence of thyroid gland invasion is low, thyroidectomy can be reserved for cases considered to be at risk as opposed to a being a routine measure for all total laryngectomies.

TABLE 14.1 Spread of laryngeal carcinoma

Primary site		Look for involvement of
Supraglottis	Epiglottis	Pre-epiglottic space
	Epiglottic petiole	Anterior commissure
	Intralaryngeal mucosa, false cords	Paraglottic space
	All	Vocal fold
		Laryngeal cartilage
Glottis	Anterior cord	Anterior commissure/ contralateral cord
	Posterior cord	Thyroid cartilage and cricothyroid membrane
	All	Arytenoid cartilage/ cricoarytenoid joint/ posterior commissure
		Paraglottic space
		Supraglottic/subglottic spread
Subglottis		Trachea
		Thyroid gland
		Cervical oesophagus

CLINICAL PRESENTATION

As with other cancers, laryngeal cancer may present with local symptoms or those due to metastatic spread to nodes or beyond. Occasionally, patients present with general systemic signs, such as weight loss or anaemia, but in laryngeal cancer these are rare in the absence of local symptoms. Paraneoplastic phenomena such as peripheral neuropathy and rashes are very rare. As a result, it is possible to provide primary care workers (and indeed the general population) with a fairly accurate idea of 'warning/red flag' symptoms that require urgent referral to an otolaryngologist.

Glottic cancer

It is fortunate that even the earliest glottic cancer alters the voice by affecting wave pattern forms over the vocal cord. Since normal voice production depends on the integrity of a six-cell thick epithelium and a delicate, jelly-like superficial lamina propria, even carcinoma *in situ* may produce significant voice change. Thus, any person with hoarseness persisting for 3 weeks or more (some would say even less time than this) should be referred urgently to an otolaryngologist for examination. The National Health Service in the UK has implemented a fast-track protocol to aid this. With increasing lesion size, maximum phonation time decreases and with the onset of cord fixation, breathiness may be superimposed, with variable degrees of aspiration. Advanced lesions may lead to airway obstruction causing progressive dyspnoea and stridor. Haemoptysis is usually associated with larger tumours. Referred otalgia (via the vagal complex) is a sinister sign suggesting deep invasion. Dysphagia and odynophagia are rare in uncomplicated glottic cancer. Neck nodes are rarely the presenting complaint; if present, they signify deep invasion and extension into the supraglottis.

Supraglottic cancer

Voice alteration is different in quality from that seen with glottic and subglottic cancer. Small supraglottic lesions not extending to the glottis may present with globus or foreign body sensation and parasthesia. If exophytic, they may cause haemoptysis. As tumour bulk increases, phonation is altered, with a 'hot potato' voice. If tumours extend to the cords, then hoarseness ensues as for glottic disease.

Further extension laterally may cause referred otalgia, odynophagia and true dysphagia. However, lesions may be asymptomatic until quite large and, as a result, first presentation with a neck lump due to cervical nodal metastasis is common.

Subglottic cancer

Again, early symptoms can be vague, with a feeling of 'globus' or foreign body sensation in the throat. Any involvement of the glottis or recurrent laryngeal nerves results in hoarseness. With paralysis, diplophonia may occur with a shortened maximum phonation time. Therefore, this diagnosis should always be considered in the possible differential causes of 'idiopathic' cord paralysis, especially in high-risk cases. Circumferential progression leads to progressive dyspnoea and stridor, with markedly shortened maximum phonation times and rapid vocal fatigue. Direct extension into the thyroid may mimic a thyroid isthmus lesion.

ASSESSMENT AND STAGING

Outpatient setting

In the outpatient setting, the larynx is best assessed using the flexible nasal laryngoscope. The procedure should be explained to patients beforehand, and in the authors' experience, the vast majority of adults tolerate the procedure very well. In most patients, a decongestant spray with a lubricated endoscope will suffice. If due care and attention is used while inserting the endoscope and the examiner ensures minimal contact with the nasal walls and stays in the lumen of the nose, the patient experiences minimal discomfort. Others may need topical anaesthetic spray to reduce the discomfort associated with the procedure. Significant information can be gained via endoscopy that will aid the decision-making process. The value of this examination should not be underestimated as this information is often complementary to what is gained during rigid endoscopy. The latter will not provide information such as cord mobility and a panoramic view of the larynx, and undue reliance should not be placed on the subsequent general anaesthetic procedure to examine the larynx.

Some centres prefer to perform outpatient endoscopy of the larynx using rigid telescopes for the superior view it provides. This requires special topical anaesthetic preparation and is less well tolerated. However, with the increasing availability of modern high-resolution flexible endoscopes that allow simultaneous recording, there is less need to use rigid telescopes for assessment. The outpatient endoscopic assessment can also direct the examiner towards additional investigations if necessary. For example, the finding of salivary pooling in the pyriform sinus in the setting of a small glottic tumour should trigger concern and prompt examination of the hypopharynx and upper oesophagus.

Laryngeal dysplasia (LD) is commonly seen in the glottis, but can be seen virtually anywhere in the larynx. The clinical appearance is that of an inflamed, erythematous larynx, with leukoplakia or erythroleukoplakia. However, clinically abnormal areas in the larynx do not always exhibit histopathological evidence of LD and LD can be detected under the microscope in clinically normal appearing epithelium. Cancers present as proliferative, infiltrative lesions or a mix of both. These are easily recognized as abnormalities on endoscopic examination. Uncommonly, malignancies, usually non-squamous cancers, can present as submucosal masses. The abnormality caused by these lesions can be subtle and may be missed on casual inspection.

Imaging

Imaging for laryngeal mass lesions should include as a minimum cross-sectional imaging for all tumour stages. Options include computed tomographic (CT) or magnetic resonance imaging (MRI), with the chest being imaged too. This is dealt with in greater detail in Chapter 37, Imaging of the neck. MRI scans have higher sensitivity than CT scans in assessing cartilage invasion. Both imaging modalities have their own advantages and drawbacks and this is also discussed in detail in Chapter 37, Imaging of the neck.

Assessment under general anaesthesia

Rigid endoscopic assessment should not only assess the extent of the tumour and take a biopsy, but also be done by a surgeon who can make the decision as to whether the tumour can be resected transorally. Anatomical constraints may make even small tumours not easily resectable. In addition, the judgement about whether special anaesthetic measures may be needed during the surgery (e.g. jet ventilation) will also need to be made and it is often helpful to do this with an anaesthetist who will be able to provide the service.

Submucosal and subglottic mass lesions can be difficult to biopsy. In these instances, an incision on the mass using microlaryngeal instruments, or preferably with a laser, will open into the abnormal tissue enabling a representative biopsy.

All excised samples should be appropriately labelled and if necessary, mounted on suitable media and orientated for the pathologist.

Staging

The staging of laryngeal cancer is discussed in detail in Chapter 4, Staging of head and neck cancer.

LARYNGEAL PREMALIGNANCY

LD has a reported incidence of between 2 and 10 lesions per 100 000 population.[18] The clinical significance LD, also known as laryngeal intraepithelial neoplasia, lies in its propensity for malignant transformation.

The 4th edition of the *World Health Organisation Classification of Head and Neck Tumours*, published in 2017, has adopted a two-tier system, based on

the morphological criteria of the amended Ljubljana Classification, where the lesions are called Squamous Intraepithelial Lesions (SIL): low-grade SILs and high-grade SILs.[19] Reported malignant transformation rates vary between 11% and 25%, but identifying which patients will transform is impossible. Given the above issues with clinical and pathological diagnosis, there is no universal consensus in the investigation and treatment of this condition. Therefore, management practices vary significantly.

The British Association of Otolaryngologists Head and Neck Surgeons have generated consensus on the management of this condition through a national survey and a joint meeting between surgeons and pathologists. The following sections will summarize these consensus guidelines, while recognizing that high-level evidence does not exist and that practices will differ based on local service arrangements and geography.

In larger centres, it is preferable if there is a nominated or a defined number of surgeons providing LD management service. It is also desirable that surgeons managing this condition have received appropriate training in laryngology. Severe dysplasia is preferably managed by personnel with expertise in head and neck cancer management.

All efforts should be made to reduce risk factors. Patients should be counselled regarding tobacco use, especially smoking in this setting. Patients who have symptoms of laryngopharyngeal reflux should also be counselled about anti-reflux measures; this may or may not include proton pump inhibitors.

LESIONS THAT HAVE NOT BEEN PREVIOUSLY TREATED

In patients who have been diagnosed to have LD following an initial biopsy, but have had no previous treatment, these are suggested management principles.

1. The overall appearance of the lesion (single, multiple or confluent) should be the most important factor in deciding management.
   - All visible single and multiple foci should be completely excised.
   - Widespread, confluent leukoplakia should be mapped using multiple biopsies. Following mapping, a staged resection should be offered if feasible. There should be a low threshold for re-biopsy in the presence of widespread disease.
   - All biopsies, including from multiple foci, should be mounted on suitable media for orientation before sending for pathological examination.
   - The general fitness of the patient will play a role in decision making.
2. Documentation in theatre
   - Intra-operative photographs should be performed before surgery and of the post-operative larynx.
   - Assessment during general anaesthesia should include palpation of the vocal cord.
   - Where possible, the intra-operative photographs should be shared with pathologists.
   - The details of type of biopsy (incisional or excisional; if mapping biopsies, identify them in the pictures) should be stated.
   - The technique and extent of resection should be documented.
   - The procedure should be categorized according to the European Laryngological Society classification.
3. Excision technique
   There is no gold standard in the tool used to resect the LD lesion. However, cold steel or laser resection is recommended over monopolar cautery
   - If laser excision is contemplated, carbon dioxide laser is recommended owing to the laser properties enabling minimal penetration, thus reducing collateral damage.
   - Laser ablation (i.e. laser used on the surface of the lesion to destroy the epithelium rather than excising it) is discouraged as no specimen will be available for diagnosis and there is a higher risk of damage to the voice.
   - Vocal cord stripping is not recommended at all owing to the high risk of damage to the vocal cord.
   - Radiotherapy should be offered only in rare circumstances for patients where there is very high risk/suspicion of conversion to malignancy and surgical resection is not possible owing to patient or tumour factors.
4. The histology should be studied in the context of the clinical findings post-operatively. If there is a report of severe dysplasia and the follow-up endoscopy shows a proliferative lesion, the patient should be re-biopsied at the earliest opportunity. The presence of dysplasia at the margins should not be of great concern, especially in mild dysplasia. This is not an indication for a repeat excision.

Figure 14.1 shows an algorithmic approach that summarizes the above points.

Management of persistent or recurrent lesions

The management of these lesions should follow the general principles and the treatment of the initial presentation as discussed above. Additional considerations are:

- Localized mild or moderate local dysplasia should be offered re-excision.
- Widespread mild or moderate widespread dysplasia may be observed or excised.
- The decision to excise should be based on a change in appearance (heterogenous texture; erythroplakia; proliferative features) or change in symptoms.
- The effect of further resections on the patients' voice should also be taken into consideration.
- Recurrent focal severe dysplasia should be managed as a T1 laryngeal carcinoma with surgical resection (e.g. cordectomy) where possible. Radiotherapy may

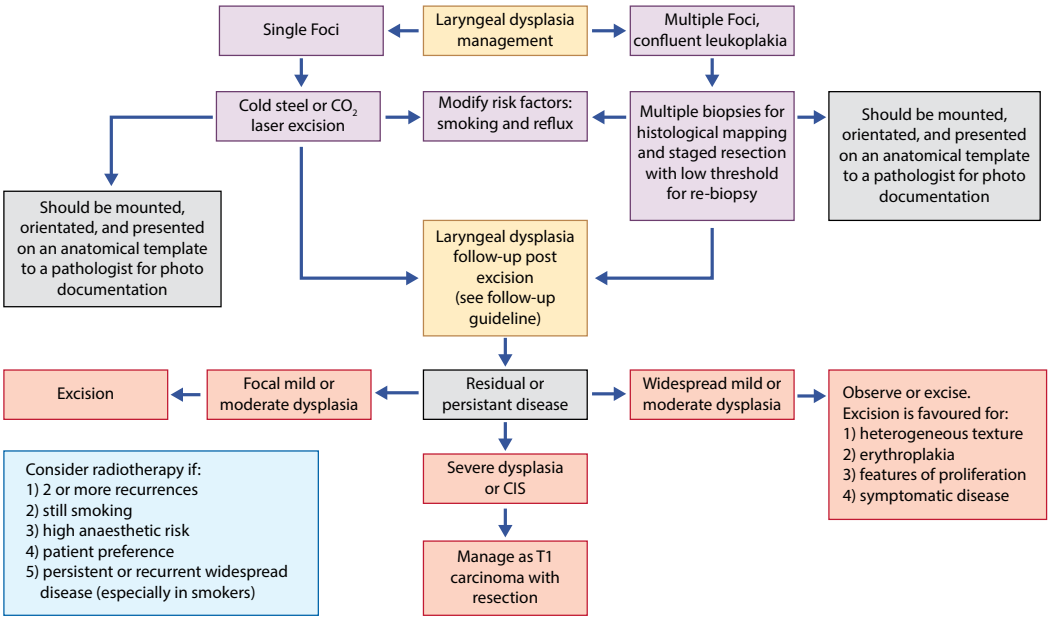


Figure 14.1 Algorithmic approach for the management of laryngeal dysplasia based on a multiprofessional consensus. (Redrawn from Cosway B, Paleri V. Laryngeal dysplasia: an evidence-based flowchart to guide management and follow up. *J Laryngol Otol*. 2015; **129**(6): 598–9.)

be considered in special circumstances only, on a case-by-case basis. Examples include patients who have had two or more recurrences, who continue to smoke, have high risk of anaesthetic complications or have poor access to the larynx.

- For persistent or recurrent widespread severe dysplasia, radiotherapy should be considered as an option.

Follow-up strategies

The recommended frequency and duration of follow-up is set out in **Figure 14.2**.

1. The ENT-UK guidelines recommend that all patients should be followed up as per the following standards:
   - Use of a flexible nasendoscope to view the larynx.
   - Colour photo documentation in the patient notes is essential.
   - Document continuing risk factors if present.
   - Stroboscopy is helpful if available, but is not necessary.
   - Follow-up of low-risk lesions can be performed by General ENT surgeons in peripheral clinics. High-risk lesions are preferably followed up by an ENT surgeon with a special interest in Head and Neck surgery or laryngology.
2. Outcomes should be assessed at baseline, 6 months and 12 months
   - Outcomes include recurrence and progression to cancer.
   - Voice outcomes should also be assessed using a patient-reported voice questionnaire.

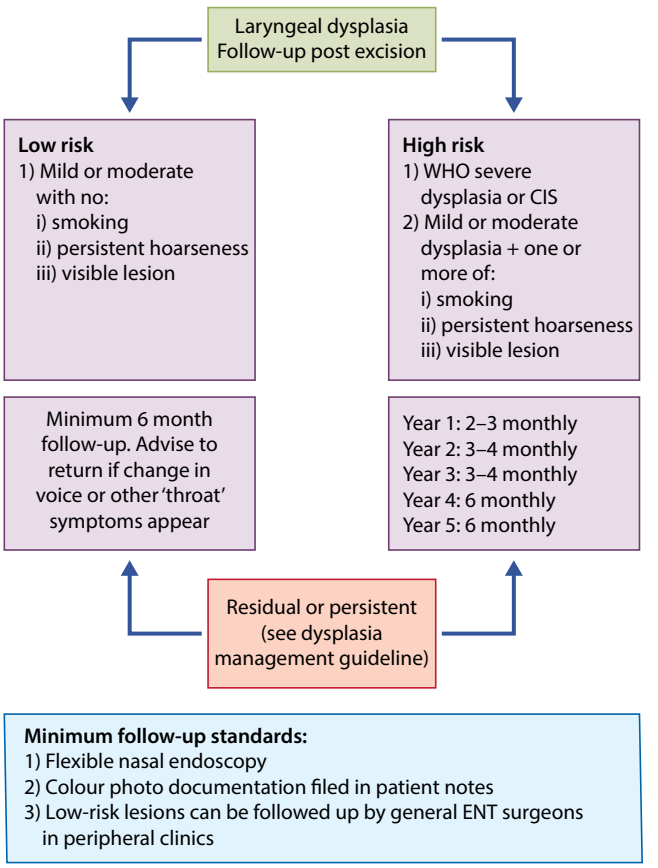


Figure 14.2 Algorithmic approach for the follow-up of laryngeal dysplasia based on a multiprofessional consensus. (Redrawn from Cosway B, Paleri V. Laryngeal dysplasia: an evidence-based flowchart to guide management and follow up. *J Laryngol Otol* 2015; **129**(6): 598–9.)

LARYNGEAL MALIGNANCIES

Decision-making

As there is evidence base to support surgical and non-surgical treatment, all decisions for management are best made in a multidisciplinary setting. The benefits of multidisciplinary working are set out in Chapter 32, Multidisciplinary team working. A multidisciplinary discussion allows the entire treating team to assess the clinical findings, radiology and pathology, along with information provided by allied healthcare personnel about the patients' function, current quality of life, preferences, comorbidity and psychosocial context. In combination, all the above are invaluable in making the appropriate treatment choice.

Management of early stage laryngeal cancers

TREATMENT PHILOSOPHY

Function and survival

Although randomized data do not exist, most practising surgeons and oncologists believe that voice outcomes are comparable for T1 glottic cancers treated by either modality, and for mid-cord lesions, this should rarely be the basis for treatment selection. Even in patients who undergo resections that are type III cordectomy or more advanced, vocal function routinely returns to pre-operative levels following the initial healing period.[20] In a meta-analysis of 362 patients with a mean follow-up time of 47 months, where voice outcomes measured using the Vocal Handicap Inventory, no significant difference in post-treatment VHI scores were detected between radiotherapy and surgery.[21] Systematic reviews have identified no advantages in voice outcomes for patients with T1 glottic cancer treated by radiotherapy (RT) compared to transoral laser microsurgery (TLM).[21–23]

In the UK, the EaStER (Early Stage glottic cancer: Endoscopic excision or Radiotherapy) feasibility trial was set up to compare TLM with RT in laryngeal cancer staged T1, but failed to recruit the required number of patients. A detailed qualitative analysis[24] identified several reasons for failure. These included lack of consensus among investigators regarding the primary outcome, non-adherence to eligibility criteria and lack of equipoise in presenting trial information. However, the ultimate reason resulting in the failure to recruit was that patients declined to be randomized because of the largely practical benefits of TLM over RT. In particular, patients favoured TLM over RT as TLM was completed as a day-case procedure whilst RT involved several weeks of daily treatment. Moreover, recovery following TLM in T1 glottic cancers is rapid with no impact on swallowing, rapid return to normal activities and minimal impact on the voice. Given the above reasons, mid-cord lesions are largely excised by TLM and larger lesions, especially when the impact on voice is considered to be greater, are treated by RT.

It is commonly believed that in early cancers, surgery or RT as a single treatment modality, offer equivalent survival outcomes. As there is less anatomical disruption to the larynx following RT, the voice quality following treatment is superior, especially when the tumour involves the AC or extends across two sites. Thus, the choice of treatment is based on patient choices and the likelihood of advantageous voice outcomes following treatment. Warner et al.[25] updated their systematic review comparing RT, open surgery and endolaryngeal excision (with or without laser) for early (T1, T2a) glottic laryngeal cancer. Although one trial that satisfied inclusion criteria was identified, it was associated with a high risk of bias. The review concluded that all are presently accepted modalities of treatment and the published large case series of each treatment suggest that they confer similar survival advantages. In an assessment of voice quality after treatment of early vocal cord cancer, a randomized trial comparing laser surgery with radiation therapy concluded that overall voice quality between the groups was rated similar, but voice was more 'breathy' and the glottal gap was wider in patients treated with laser surgery than in those who received radiation therapy. Patients treated with radiation therapy reported less hoarseness-related inconvenience in daily living 2 years after treatment.[26, 27] The equivalence of the two modalities has been questioned by some new data. In a population-based analysis of 10 429 patients with localized laryngeal cancer (90% T1 and T2; 10% T3) from the SEER database between 1995 and 2009, Misono et al.[28] observed that while single modality treatment increased over the years (radiation or local surgery), combined modality treatment decreased, with these changes being statistically significant. Survival was analyzed by treatment modalities. Compared with radiation only, which was the reference category, patients who underwent 'local surgery only' or 'local surgery and radiation' had lower hazards of death ($P<.0006$ and $P<.0001$, respectively), with the survival differences persisting beyond 5 years of treatment. Whereas the 5-year disease specific survival rates for the 'local surgery' and 'local surgery and radiation' groups were 91% and 90% respectively, the 5-year survival rate for the 'radiation only' group was 83%.

Similar results have been produced in a database analysis for supraglottic cancers alone. Arshad et al.[29] analyzed outcomes in 2631 patients with early stage supraglottic cancer from the Surveillance, Epidemiology and End Results (SEER) database in the United States. In patients with T2N0 cancer, partial laryngeal surgery and neck dissection led to significantly better 5-year disease specific survival (86% vs 60%; HR = 0.31, $p<0.001$) and overall survival (77% vs 45%; HR = 0.36, $p<0.001$) compared to radiation therapy. These data go against the common perception that in early cancers, either modality offers equivalent survival.

Such retrospective reports, despite large numbers, have associated bias, but are hypothesis generating and clearly indicate the need to look for differences between these treatment methods in a controlled setting. However, it is highly unlikely that an adequately powered randomized controlled trial will be performed in the near future. Given the above data, the authors believe that if expertise is available and all else being equal, all patients should be offered

both treatment options with early stage cancers. The volume of data supporting better survival for the surgical arm is compelling and should be shared with patients.

ORGAN PRESERVATION AS AN ARGUMENT FOR PRIMARY SURGERY FOR EARLY LARYNGEAL CANCER

This is an important issue that is not often discussed during the decision-making process when treatment is planned for early laryngeal cancer, especially stage II. It should be recognized that T2 cancers, despite being categorized as 'early disease', have a significantly higher risk of local recurrence. This has been demonstrated in several studies. Organ preservation following the use of RT in a series of 260 patients with T2 laryngeal squamous cell carcinoma (LSCC) was 81% and 74% for T2a and T2b tumours respectively.[30] McCoul et al.[31] have shown in a meta-analysis of 21 studies (published between 1967 and 2007) that for T2a and T2b laryngeal tumours treated by radiation therapy, mean local control at 5 years was 76.2% (SD 10.2%) and 64.4% (10.2%) respectively. When four of the 21 papers from this study (n = 653) that were published in the last decade are considered separately, local 5-year control rates range between 70% and 80%, indicating no significant improvement in control rates. In a single centre[32] series of 1615 patients with laryngeal cancer of all stages, the 3-year risk of recurrence for T2 cancer was 27.3%. Thus, at least 25% and up to 30% of patients will suffer local disease recurrence when primary RT is used to treat T2 LSCC. These figures have been replicated in large population cohort studies.[33] In the patients who develop disease recurrence following RT, organ preservation is usually not feasible due to tumour and patient factors and total laryngectomy is often required, although open partial laryngectomy (OPL) (see 'Open partial laryngectomy (OPL) below) may be feasible in selected cases. Consequently, most patients who develop local recurrence of T2 LSCC following initial treatment with RT are treated with total laryngectomy, with the inevitable costs to voice and swallowing function as well as overall quality of life.

Prospective datasets suggest that between 7% and 15% of patients treated with transoral procedures for early laryngeal cancer will suffer local disease recurrence. Unlike in patients who recur following RT, a greater repertoire of re-treatment options is available (OPL, repeat TLM/TORS and/or RT) in an attempt to preserve a functioning larynx. This is demonstrated by three large case series with more than 100 patients each of T2N0 disease, with organ preservation rates of 84% to 96% are observed for T2N0 tumours.[33–35] As expected, survival rates are not different across the two modalities. A recent systematic review 48 papers pooled data from 1156 patients treated by TLM and 3191 treated with RT, showed similar local control rates.[36]

Similar high rates of laryngeal preservation are seen in series reporting the outcomes of surgery for T3 tumours of the larynx (73–83%)[35, 38] providing further support for the efficacy of this sequential organ preservation approach. As a result of these and other data, a recent review concluded that there was higher chance of laryngeal preservation if surgery was used as the initial treatment modality in T2 tumours.[39] While studies suggest that the voice outcome may be poor in surgically treated patients,[40] there is no doubt that the poorest voice results when a patient loses their larynx. It follows that the discussion to be had with the patient is whether an initial potential reduction in voice quality is acceptable to retain a fully functioning larynx.

HEALTH ECONOMICS AND EARLY GLOTTIC CANCER

Surgery for early stage laryngeal cancer has been shown to have superior cost-utility compared to RT in a meta-analysis.[41] A recent analysis compared TLM against RT in the management of early stage (T1a, T1b and T2) glottic cancer to identify the most cost-effective treatment modality within the UK National Health Service.[42] A Markov decision model was populated using data from updated systematic reviews and meta-analyses, with attributable costs from NHS sources. The study concluded that over a 10-year time horizon, RT as the initial treatment strategy was more expensive (£2654 vs £623) and less effective (quality adjusted life year (QALY) reduction of 0.141 and 0.04 in T1a and T1b-T2 laryngeal cancer respectively) than TLM. The dominance of TLM for T1a cancers was unchanged on sensitivity analysis in most modelled scenarios, while for T1b-T2 laryngeal cancers, RT became more cost-effective when TLM costs were increased and when a QALY gain was assumed for RT. In the UK, TLM is recommended as optimal treatment for T1a glottic tumours, unless robust contraindications exist.

A cost-effectiveness analysis considering the Canadian healthcare system[43] found TLM to dominate RT with higher QALYs and lower costs. A study of the itemized average costs of RT and TLM in the American healthcare system in 2001 showed RT to be 15.5 times more costly.[44] Using the 5-year survival rate as the 'effect' in a cost-effectiveness analysis, Diaz-de-Cerio et al.[45] found that TLM offered a saving of €1342.68 per year in the Spanish healthcare setting, concluding that TLM was the dominant option for T1 and T2 glottic cancers.

TREATMENT OPTIONS

There has been a significant expansion in the repertoire of surgical procedures used to treat early laryngeal cancer.

Transoral partial laryngectomy

Newer developments permit partial laryngectomy to be performed through transoral approaches. TLM is very commonly used for early cancer of the laryngeal glottis and the supraglottis, with widespread expertise and has also been shown in several controlled series to provide excellent oncological and functional outcomes,[35] comparable to OPL.[46] Centres with expertise in this procedure have moved to a stage where they offer patients with this stage of disease only surgery, with consistently excellent long-term results.[35, 47, 48] TLM is discussed in detail in Chapters 22, Transoral laser microsurgery and 23, Anatomy as applied to transoral surgery. The other

method to perform transoral partial laryngectomy is with the assistance of a robot, used primarily for supraglottic cancers; transoral robotic surgery is dealt in greater detail in Chapter 29, Applications of robotics in head and neck practice.

Open partial laryngectomy (OPL)

Although OPL has been in use in Europe (especially France and Spain) for many years, this procedure has not gained wide acceptance in many countries. Reasons include easier access to radiation therapy services and concerns about post-operative function, which has consequently led to loss of expertise. However, recent publications confirm good to excellent long-term functional and oncological outcome for these procedures,[49] and refinement of the procedure[50] that leads to consistent results. A more detailed treatment of OPL can be found in Chapter 27, Open conservation surgery for laryngeal cancer.

RADIATION THERAPY

RT as a single modality offers an alternative to organ preserving surgical options in the treatment of early LSCC (glottic and supraglottic). The long-term local control rates for early glottic carcinomas are similar to organ preserving surgical approaches (TLM). RT is preferred in most centres in the UK and the United States, where the tumour involves AC and in T2 glottic tumours, largely due to better functional outcomes and to a lesser extent due to the low availability of surgical expertise. This modality is also the preferred option in patients with poor access for surgery and/or high risk for general anaesthesia.

The long-term local control rates following RT alone for early supraglottic carcinomas are also similar to surgery with 5-year local control rates of 100% for T1 and 86% for T2.[51] With increasing expertise in minimal access surgery, the proportion of patients treated with surgery is likely to increase.

TREATMENT PRINCIPLES

Transoral laser microsurgery

Glottic cancers: The standard of care for surgical treatment of mid-cord glottic cancers is TLM. For mid-cord lesions staged T1a, TLM excision has a very high cure rate[23,27] with the undeniable advantage of higher laryngeal preservation rates[27,52] and is commonly recommended in most MDTs where expertise exists. TLM to excise T1a lesions is easily taught and learnt, and the treatment process is rapid and preferred by patients,[24] with health economic benefits.[42]

TLM is less commonly used for T1 cancers that involve the AC and for T2 cancers as the impact of surgical resection on the voice is considered to be greater, although cure rates are at least equivalent, if not higher than those achieved by radiation therapy (**Tables 14.2** and **14.3**). The suitability of AC lesions for TLM has been debated in the literature, with some reports suggesting that AC location has an impact on prognosis,[53–56] while others do not.[57] A systematic review[58] of T1b tumours treated by either modality showed a trend towards improved local control when treated with RT, with the caveat that this finding was based on a limited number of published outcomes (n = 194).

All glottic cancers resected by the TLM approach should be classified as per the European Laryngological Society (ELS) system,[59] which describes six types of cordectomy based on the extent of resection of the vocal cord and the adjoining structures (**Table 14.4**).

It is well recognized that AC lesions can exhibit cartilage invasion in up to 20% of cases at presentation.[60,61]

It is important that the resection specimens are orientated for the pathologist; small specimens sent in a fixative solution can cause shrinkage and curling of the tissue hindering accurate histological interpretation. The techniques used to orientate larger specimens are not effective and thus should be mounted and orientated on suitable media. A popular

TABLE 14.2 Literature review of post-treatment status for anterior commissure SCC – a comparison between surgical outcomes versus radiotherapy

Study (Anterior commissure SCC)	Primary Treatment	Local control rate	Laryngeal preservation rate	Disease-free survival	Overall survival
Mendelsohn et al.[20]	LASER	83.3%	93.3%	96.7%	96.7%
	RT	NA	NA	NA	NA
O'Hara et al.[58]	LASER	76.8%	NA	NA	NA
	RT	86.2%	NA	NA	NA
Taylor et al.[62]	LASER	95%*	100%*	88.7%*	94.1%*
	RT	85.9%*	85%*	85.9%*	94.8%*
Kerr et al.[40]	LASER	99%	100%*	99% +/-2%	91% +/- 3%
	RT	99%	79%*	99% +/- 1%	90% +/- 4%
Bradley et al.[63]	LASER	84%^	93%^	73%*^	NA
	RT	90%	NA	NA	NA

RT – radiotherapy; * - p values>0.05; NA – 'non-applicable' as the authors did not have any considerations for these criteria; ^ - Steiner et al, 2004.

TABLE 14.3 Literature review of post-treatment status for early glottic SCC – a comparison between surgical outcomes versus radiotherapy

Study	Primary Treatment	Local control rate	Laryngeal preservation rate	Disease-free survival
Wilkie et al.[64]	LASER	92%	98%	86%
	RT	NA	NA	NA
Kerr et al.[40]	LASER	NA	100%	99%
	RT	NA	92%	99%
Hartl et al.[65]	LASER	94%	96%	89%
	RT	NA	NA	NA
Peretti et al.[66]	LASER	92.7%	97.1%	81.3%
	RT	NA	NA	NA
Chera et al.[30]	LASER	NA	NA	NA
	RT	94%	95%	97%
Schrijvers et al.[52]	LASER	71%	95%	NA
	RT	73%	77%	NA
Krengli et al.[67]	LASER	96%	96%	95.9%
	RT	90%	91.2%	91.3%
Smith et al.[68]	LASER	NA	97.4%	76.9%
	RT	NA	96.3%	88.9%
Ambrosch et al.[34]	LASER	99%	98.8%	NA
	RT	NA	NA	NA
Spector et al.[69]	LASER	77%	90.2%	77%
	RT	90%	85.1%	85%
Rosier et al.[70]	LASER	88%	NA	83.9%
	RT	90%	NA	90.2%
Foote et al.[71]	LASER	NA	92.5%	87.7%
	RT	NA	94.5%	94.7%

option is to use dehydrated cucumber as a mount with the specimen anchored to it by tissue glue (**Figure 14.3**).[72]

It should be recognized that for the specimens resected by TLM will have much smaller margins than traditional open surgery, with margins of the order of a millimetre being appropriate, which should not be misinterpreted as close or positive margins. Thus, the pathologist should be fully apprised of the nature of the resection and there should be clear channels of communication between the surgeon and the pathologist for appropriate reporting of the resection margins. The authors cannot emphasize enough the importance of clinico-pathological correlation in transoral resections. This is often an area of contention and guidelines for management after TLM have been published by the British Association of Otolaryngologists — Head and Neck Surgeons.[73] These are summarized in **Box 14.1**.

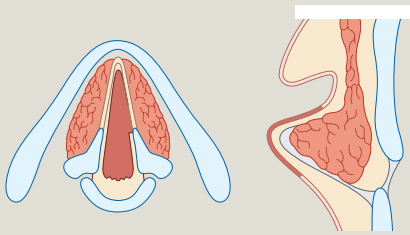
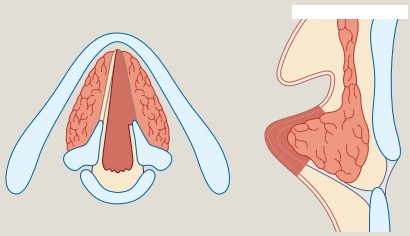
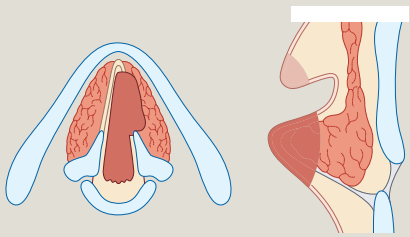
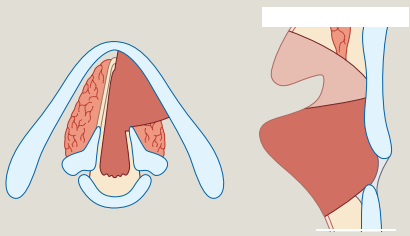
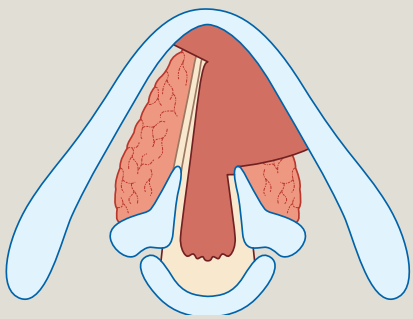
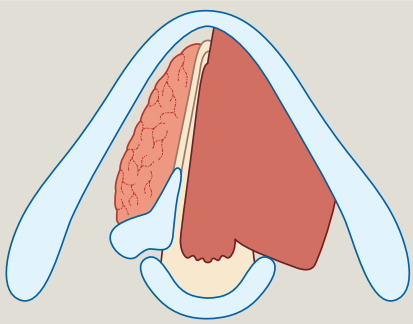
Supraglottic cancers: All supraglottic cancers resected by a transoral approach should be classified as per the ELS system,[74] which describes four types of supraglottic laryngectomy based on the extent of resection (**Table 14.5**). As stated earlier, it is important that all resections be orientated for the pathologist. Unlike glottic cancer, where possible, a conscious effort should be made to achieve surgical margins of at least 5 mm during resection. Further patient side biopsies can be sent for confirmation of the margin status.

Unlike glottic cancers, patients following transoral resections for supraglottic tumours can be expected to have significant swallowing dysfunction in the early stages, even up to 6 weeks at times. Appropriate swallow assessment, therapy and supplemental feeding may be necessary. However, the author's experience and the literature suggest that the swallow outcome is invariably favourable and patients achieve very good functional swallow.[75, 76]

Open partial laryngectomy

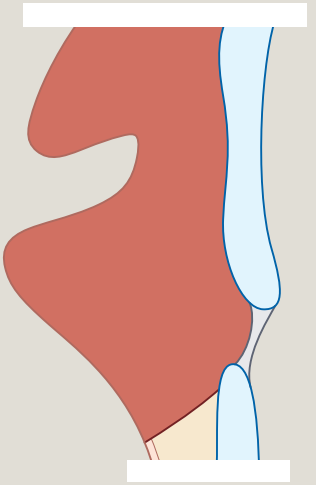
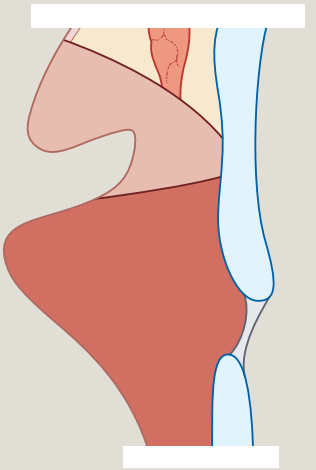
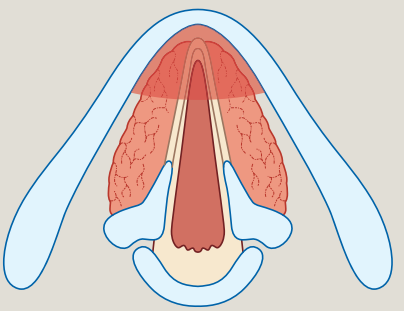
There is little debate about the oncological efficacy of OPL as primary treatment for early laryngeal cancer. The relatively poor functional outcome has been the deterrent to wide use of this procedure. A systematic review by Thomas et al.[49] on the outcome of surgically treated laryngeal cancer showed a pooled local control rate at 24 months from 5061 patients to be 89.8% (95% CI 88.3–91.2), a pooled overall survival of 79.7% (n = 3967; 95% CI 76.5–782.8) and pooled mean disease-free survival of 84.8% (n = 2344; 95% CI 80.6–88.7). These figures are comparable to any other treatment modality, despite the fact that a substantial proportion of the cohort in the study had T3 disease. Some of the studies with large cohorts from high-volume centres are

TABLE 14.4 European Laryngological Society classification of cordectomies for glottic carcinomas[59]

Definition	Type	Description
Subepithelial cordectomy	I 	Resection of the vocal fold epithelium passing through the superficial layer of the lamina propria
Subligamental cordectomy	II 	Resection of the epithelium, Reinke's space and the vocal ligament
Transmuscular cordectomy	III 	Resection of the vocal fold down through vocalis muscle
Total cordectomy	IV 	Resection of the cord, which extends form the vocal process to the anterior commissure. The depth of the surgical margins reaches or includes the internal perichondrium of the thyroid ala
Extended total cordectomy	Va 	Resection includes the contralateral vocal fold and the anterior commissure
	Vb 	Resection includes the arytenoids

(Continued)

TABLE 14.4 *(Continued)* European Laryngological Society classification of cordectomies for glottic carcinomas[59]

Definition	Type	Description
	Vc 	Resection includes the subglottis
	Vd 	Resection includes the ventricle and false cords
Anterior commissurectomy	VI 	Resection of the anterior commissure with bilateral anterior cordectomy; may include the subglottic mucosa and the cricothyroid membrane

summarized in the table below. OPL has been used in the past for supraglottic cancers with significant success rates.[49] It is recommended that the ELS system of classification of open horizontal laryngectomy be used by surgical practitioners to collate data and report on this technique.[77] However, as the procedure involves disruption of the neck musculature and also sensory supply to the pharynx, functional outcomes were even less predictable than with resections for glottic cancer. With the emergence of transoral approaches, OPL is less used as a primary procedure.

Transoral robotic surgery (TORS)

Glottis: Early experience with this modality suggests equivalent oncologic control rates as for TLM.[78, 79] However, the advantages of a TORS approach for glottic tumours are yet to be defined.

Supraglottis: TORS has been a useful addition to the surgical armamentarium in the management of supraglottic tumours. The high-definition three-dimensional vision of the operating field, wristed movement with 7 degrees of freedom and the ability to work without the target

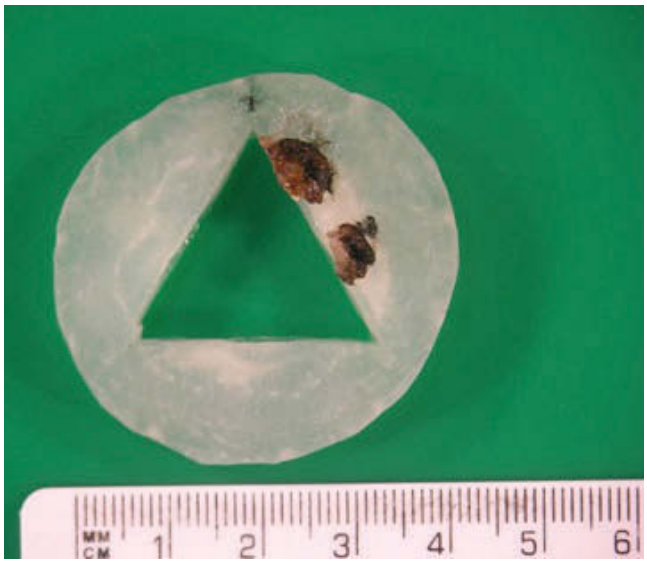


Figure 14.3 Cordectomy specimen mounted on dehydrated cucumber.

BOX 14.1 Post-resection management following cordectomy for early laryngeal cancer

1. All specimens must be orientated and mounted for histological analysis.
2. Terminology such as 'complete excision', 'close margins' and 'incomplete excision' are misleading. It is advisable for the pathologist to precisely specify the sites on the orientated specimen where the margins are less than 1 mm. This will help in planning a second look and during follow-up.
3. Based on the pathologist's report, the following actions are recommended:
   (i) If the resection margins are considered surgically adequate and are clear by a millimetre or more on histology, no second look is warranted. Routine clinical monitoring will suffice.
   (ii) If the surgical margins are not in doubt but the histology shows tumour at the margins, a second look is recommended 6–8 weeks later.
   (iii) If the surgeon has concerns about resection margins and residual tumour is confirmed on histological analysis, the feasibility of further TLM resection should be considered.

Future management should be discussed at the MDT meeting and careful consideration given to alternative non-endoscopic treatment options.

being in line of sight (as for laser microsurgery) has made robotic supraglottic laryngectomy a procedure that can be taught and learnt with greater ease than TLM procedures (**Figure 14.4**). As for TLM procedures, support systems for the post-operative swallowing dysfunction should be in place. As **Table 14.7** suggests, outcome data are comparable to those performed by the established TLM techniques.

Neck management

T1 glottic cancer usually presents with no metastatic lymphadenopathy and the risk of occult nodes are very small. Thus, treatment for the primary site alone will suffice. T2 tumours also are less prone to metastatic spread, but given the risk of occult spread of ~7%, there is no consensus on whether the neck should be treated in this setting.

With supraglottic, unlike glottic cancers the neck will almost always need to be addressed even if there is no clinical or radiological evidence of disease. The incidence of occult neck metastases is well over 15%. Exceptions to this rule might be small cancers of the tip of the epiglottis with minimal invasion, or for salivary malignancies in this region.

Radiation therapy

Glottic carcinoma: RT is delivered using megavoltage photons (4 to 6MV), the target volume encompasses the primary tumour. The regional lymph nodes are not treated due to low risk of lymph node metastasis. The treatment is usually delivered using two lateral fields covering the laryngeal skeleton from thyroid notch superiorly to the inferior border of cricoid. The field size ranges from 4 × 4 cm to 5 × 5 cm, with larger field size for T2 tumours, depending on the extent of tumour. The most commonly used fractionation regime in the UK is 50 to 55 Gy in 16 to 20 daily fractions over 3 to 4 weeks. Yamazaki et al. reported a prospective randomized trial in patients with T1N0M0 glottic carcinoma receiving definitive radiation treatment. The study compared two different doses per fraction (2 Gy/fraction Vs 2.25 Gy/fraction). The 5-year local control rates were 77% after 2 Gy per fraction and 92% after 2.25 Gy per fraction with no difference in either acute or late toxicity.[84]

Supraglottis: The target volume for radiation treatment encompasses the primary tumour and lymph nodes bilaterally (Level II–IVa) due to high risk of microscopic lymph node metastasis. The at risk nodal levels are treated to a reduced dose (prophylactic dose). The fractionation regime commonly used is as for glottic carcinomas. Alternatively, a regime of 65 Gy in 30 fractions over 6 weeks is used.

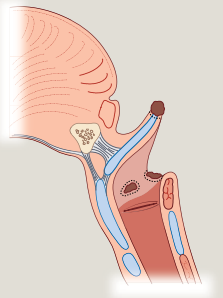
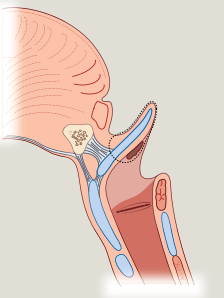
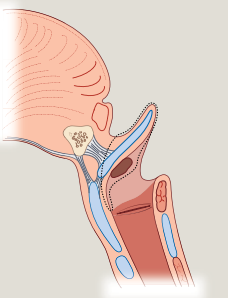
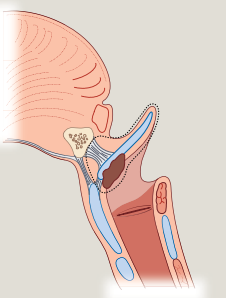
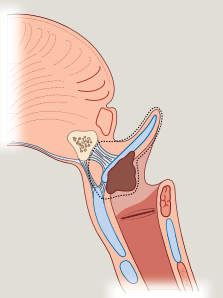
Management of T3 laryngeal cancer

TREATMENT PHILOSOPHY

Functional issues

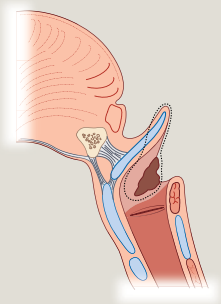
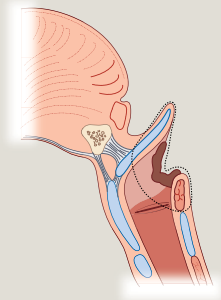
Physicians treating laryngeal cancer have always assumed that laryngeal preservation is a priority for all patients. In 1981, when total laryngectomy was the standard of care, McNeil et al. published a landmark study[85] scrutinizing the trade-off between quantity and quality of life faced by patients diagnosed with locally advanced laryngeal cancer. The utility analysis was performed on 37 healthy volunteers based on the assumption that RT was associated with a poorer survival, but a better voice outcome, while laryngectomy achieved an improved survival at the expense of an artificial voice. The study showed that not everyone valued survival at any price and that survival may not be the most important outcome for all patients. This study has no doubt contributed to the organ preservation

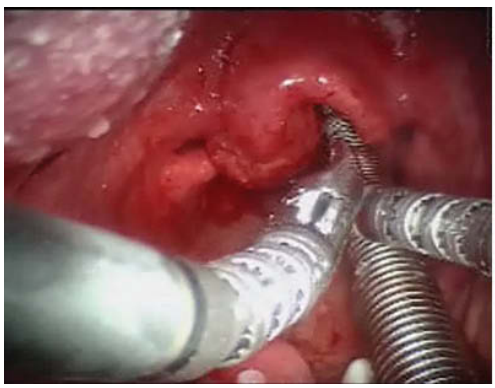
TABLE 14.5 European Laryngological Society classification of transoral resections for supraglottic carcinomas[74]

Definition	Type		Indication and Description
Limited excision	I		Excision of small superficial tumours anywhere on the supraglottis
Medial supraglottic laryngectomy with partial resection of the pre-epiglottic space	IIa		Tumours of laryngeal surface of epiglottis located above the hyoid bone: resection includes the suprahyoid epiglottis
	IIb		Tumours extending below the hyoid: resection includes a total epiglottectomy
Medial supraglottic laryngectomy with resection of the pre-epiglottic space	IIIa		Tumours extending to petiole of epiglottis: resection must include the pre-epiglottic space
	IIIb		Tumours of the infrahyoid epiglottis extending to the ventricular fold: resection includes ventricular folds dissected from the thyroid cartilage

(Continued)

TABLE 14.5 *(Continued)* European Laryngological Society classification of transoral resections for supraglottic carcinomas[74]

Definition	Type		Indication and Description
Lateral supraglottic laryngectomy	IVa		Tumours of the threefolds' region: resection of free edge of the epiglottis, the aryepiglottic fold, the pharyngo-aryepiglottic fold and the ventricular fold
	IVb		Tumour extending to arytenoids: resection includes the arytenoids and inner/medial or anterior wall of the pyriform fossa



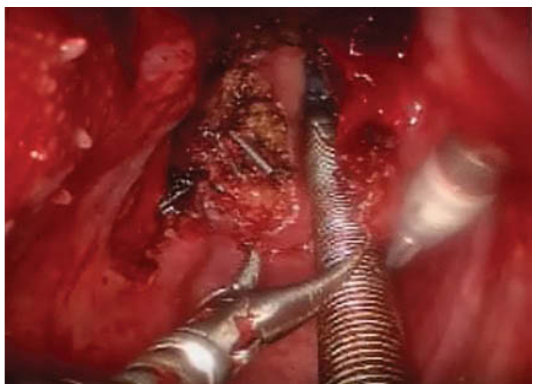


Figure 14.4 Transoral robotic supraglottic laryngectomy for a T2N0 lesion.

TABLE 14.6 Recommended treatments for early glottic cancer

T stage	1st choice	2nd choice	3rd choice
T1a	TLM	RT	OPL
T1b	RT or TLM*	OPL	-
T2a	RT or TLM*	OPL	-
T2b	(C)RT	TLM	OPL

* based on patient choice, local expertise, tumour and patient factors.

trials in the 1990s and the first decade of this millennium (see below). Although quality-of-life comparisons between patient groups treated with total laryngectomy or chemoradiation show differences in functional subscales, the overall QOL scores of both groups seem similar.[86, 87] Clearly significant clinical experience has been accrued since the organ preservation protocols have been implemented across the world. When Laccourreye et al.[88] polled 163 otorhinolaryngologists about the percentage chance of cure that they would be prepared to trade-off to preserve their larynx when faced with advanced stage laryngeal cancer, the professionals were almost equally

TABLE 14.7 Literature review of post-treatment status for early supraglottic laryngeal SCC – a comparison between surgical outcomes versus radiotherapy

Study (early supraglottic SCC)	Primary Treatment	Local control rate	Laryngeal preservation rate	Disease free survival	Overall survival
Swanson[80]	LASER	86%	NA	NA	NA
	RT	70%	NA	NA	63%
Canis et al.[81]	LASER	85%	96%	92%	76%
	RT	NA	NA	NA	NA
Motta et al.[82]	LASER	63%	85.4%	94%	88%
	RT	NA	NA	NA	NA
Ambrosch et al.[83]	LASER	89%	NA	83%	76%
	RT	NA	NA	NA	NA

TABLE 14.8 Recommended treatments for early supraglottic cancer

T stage	1st choice	2nd choice
T1	RT or TLM/TORS*	OPL
T2	RT or TLM/TORS*	OPL

* based on patient choice, local expertise, tumour and patient factors.

divided between total laryngectomy and larynx preservation. These authors[89] also performed a similar questionnaire survey on 269 patients attending the otolaryngology service for various problems and concluded that laryngeal preservation is not a major objective of treatment shared by patients filling a questionnaire devoted to the choice of treatment when facing an advanced laryngeal cancer.

Hamilton et al.[90] replicated the work by McNeil et al.[85] in a more robust fashion. They developed four health state descriptors representing total laryngectomy or chemoradiotherapy with either optimal outcome or with complications. They recruited 114 participants demographically matched to the head and neck cancer population, and asked them to rank the outcome scenarios, assign utility values to each health state using time trade-off and rate the importance of survival on treatment choice. This study concluded that the functional outcome of treatment was a greater determinant of a laryngeal cancer health state utility value than treatment modality and that in many individuals, larynx preservation may not be the primary consideration for treatment selection. This puts in perspective the discussion in the next section on treatment choices for these patients.

RECURRENCE, SURVIVAL AND CONTROVERSY AROUND TREATMENT CHOICES

In the latter part of the 20th century, the standard treatment for T3 laryngeal cancer was total laryngectomy. Indeed, no study has shown improvements in local control and survival compared to total laryngectomy. The landmark Veterans Affairs study[91] compared induction chemotherapy followed by radiation to total laryngectomy and is to date the only study to have compared surgical management with non-surgical management. The study recruited 332 patients with stage III or IV laryngeal squamous carcinoma who were randomized to either three cycles of chemotherapy followed by RT or surgery and RT. In the non-surgical arm there was an assessment after two cycles of chemotherapy. Patients who did not clinically respond crossed over the surgical arm and were treated by total laryngectomy. The study reported comparable survival in both groups of 68% at 2 years. Overall the laryngeal preservation group was 64% in those treated in the non-surgical arm. This study was the first to suggest that non-surgical treatment was a valid option for stage III and IV laryngeal tumours. The Veterans Affairs study had a higher proportion of supraglottic tumours compared to glottic tumours (208 vs 124). The majority were T3 (216) tumours, with a Karnofsky score of >80 in 253 of the patients. Patients who eventually needed a laryngectomy in the non-surgical arm had glottic tumours, fixed vocal cords, gross cartilage involvement and stage IV or T4 cancers. The above factors should be taken into consideration when interpreting the results.

The Intergroup Radiation Therapy Oncology Group (RTOG) 91–11 trial[92] randomized 547 patients to one of the three study groups, which included RT only, induction chemotherapy followed by radiation (ICRT) and radiotherapy with concurrent cisplatin (CRT). The study found that at 2 years, a statistically higher proportion of patients who received CRT had an intact larynx after RT (88%) compared to ICRT (75% P = 0.005) or RT (70%, P<0.001). The rate of locoregional control was also significantly better with CRT (78 percent, vs 61 percent with ICRT and 56 percent with RT only). This trial showed that in suitably selected patients, the addition of chemotherapy concurrently to RT enhanced chances of laryngeal preservation significantly, while not showing a decrease in the overall survival. Subsequently, longer term outcomes for this study with a median follow up of 10.8 years have been published.[93] The long-term study confirmed that both chemotherapy regimens significantly improved organ preservation. Although overall survival did not differ significantly across the groups, there was a trend towards a worse outcome with CRT relative to ICRT. In addition,

the study also demonstrated a statistically significant higher percentage of deaths not attributed to larynx cancer or treatment in the CRT arm (30.8%) than the ICRT (20.8%) or the RT arm (16.9%). The toxicity of the CRT was not insignificant. The CRT arm experienced a 43% rate of severe late complications, including an 18% rate of pharyngeal dysfunction, a 25% rate of laryngeal dysfunction, a 7% rate of death due to the treatment protocol and a high rate of complications following salvage laryngectomy.

Since the publication of the above two studies, several commentators have expressed concerns about the generalization of the trial results to all patients with advanced laryngeal cancer[94, 95] without a full appreciation of the caveats of this approach. The undoubted advantages to organ preservation should be placed and understood in the context of the inclusion criteria to this trial, which have been discussed in an elegant editorial.[96] Over 40% of the patients in the two studies had mobile vocal cords (48% in the VA study and 42% in the RTOG 91–11 study); it is well recognized that cord fixity has an adverse prognosis compared to mobile cords and these patients would have needed a total laryngectomy anyway. The trial participants included a proportion of T2 patients, who could potentially be treated by partial laryngectomy, thus avoiding a permanent stoma. The lack of a surgical arm has been a drawback of this trial, especially given the long-term follow-up data suggesting more causes of non-cancer deaths in the CRT arm. It is important to recognize that several studies[47, 49, 97, 98] showing comparable mature outcomes in patients with T3 cancer who received open or transoral partial laryngectomy as the primary management.

Large database analyses have suggested that a primary non-surgical treatment may have an adverse effect on survival. Hoffman et al.[99] analyzed data from 158 426 cases of laryngeal squamous cell carcinoma (excluding verrucous carcinoma) diagnosed between the years 1985 and 2001 from the US National Cancer Data Base. This review of data showed decline in the 5-year relative survival between the 1985–1990 period and the 1994–1996 period among glottic and supraglottic cancers classified as T3N0M0. Initial treatment of T3N0M0 laryngeal cancer (all sites) in the 1994–1996 period resulted in poor 5-year relative survival for those receiving either chemoradiation (59.2%) or irradiation alone (42.7%) when compared with that of patients after surgery with irradiation (65.2%) and surgery alone (63.3%); there was no difference during this period for the subset of T3N0M0 glottic cancers initially treated with either chemoradiation or surgery with irradiation. In a subsequent SEER analysis, Chen et al.[100] showed that between 1985 and 2007, the use of CRT increased from <7% to 45%, whereas the use of total laryngectomy decreased from 42% to 32% in patients with advanced staged cancer. The 4-year survival rates for patients with advanced laryngeal cancer treated with total laryngectomy, CRT, and RT were 51%, 48% and 38% respectively despite patients receiving CRT being used in younger patients from higher socioeconomic groups.

Megwalu et al.[101] studied a cohort of 5394 patients who received a diagnosis of stage III or IV laryngeal squamous cell carcinoma between 1992 and 2009. Data were extracted from the Surveillance, Epidemiology, and End Results (SEER) Database in the US. They found that patients who received surgical therapy had better 2- and 5-year disease-specific survival (70% vs 64% and 55% vs 51%, respectively; $P < .001$) and 2- and 5-year overall survival (64% vs 57% and 44% vs 39%, respectively; $P < .001$) than patients who received non-surgical therapy. The difference in DSS and OS between treatment groups remained statistically different after stratification by year-of-diagnosis cohorts. Multivariate analysis showed non-surgical patients to suffer worse hazard of disease-specific survival (1.33 [95% CI, 1.21–1.45]) and overall survival (1.32 [95% CI, 1.22–1.43]) after adjustment for other variables. The authors concluded that surgical therapy leads to better survival outcomes than non-surgical therapy for patients with advanced laryngeal cancer. A further analysis[102] of 487 patients with T3 laryngeal tumours alone from the SEER registry and Medicare databases showed adjusted hazard ratio for OS of 0.68 (95% CI, 0.49–0.94) for patients receiving surgery alone vs non-surgical management and 0.75 (95% CI, 0.57–0.98) for patients receiving surgery plus adjuvant treatment vs non-surgical management.

The above analyses could be considered to favour surgery on the basis of less comorbidity in the surgical group. However, in an investigation into the prevalence of comorbidity in surgical vs non-surgical patients in 16 489 cases of advanced laryngeal cancer from the national cancer database, Zhu et al.[103] found that patients with comorbidity were less likely to receive chemoradiation than subtotal or total laryngectomy, with a risk ratio (RR) of 0.84 (95% CI, 0.81–0.87) for patients with one or more comorbidities compared with those without any comorbidity, after controlling for factors such as tumour stage, age, race/ethnicity, insurance and socioeconomic status. A recent systematic review[104] echoes the above points about heterogeneity in staging, anatomical subsite and heterogeneity in patient cohorts, concluding that CRT should not be used as a 'One size fits all' approach for T3 cancers.

The above discussion brings to the fore the question that surgery has not been directly compared to various forms of primary non-surgical therapy. Organ preservation can only be considered for an organ which is fulfilling its functions. Thus, a dysfunctional larynx where the airway is compromised, or where the tumour bulk causes significant dysphagia needing tube feeding are circumstances where organ preservation strategies should not be considered, even if the tumour stage and extent makes it suitable. These are echoed by the recommendations of the Larynx Preservation Consensus Panel.[105]

While the VA trial showed no improvement in survival following primary surgery for patients with stage III and IV laryngeal cancers, there is broad consensus in the literature that primary surgery for T3 tumours offers the best chance for locoregional control. Two single centre studies[106, 107] of stage III or IV laryngeal SCC with

substantial numbers have shown that surgical treatment was associated with statistically significant superior locoregional control rates (16% to 20%), but not in overall survival with a primary surgical option. In a single-centre large series of 1615 patients with laryngeal cancer of all stages,[32] the 3-year risk of recurrence was highest for T3 (35.8%) laryngeal cancer. Of the 368 patients with recurrent disease, 271 (74%) were managed by RT as primary treatment.

However, a meta-analysis[108] of outcomes following primary surgery vs non-surgical treatment for advanced-stage laryngeal cancer arrived at different conclusions. Data from 16 retrospective studies involving 8308 patients (4478 in the TL group and 3701 in the non-surgical group) showed that TL had better 2- and 5-year overall survival (OR 2.79, 95% CI 1.85–4.23 and OR 1.52, 95% CI 1.09–2.14). Interestingly, there were no significant differences between TL and NOP for 5-year local control. This indicates the heterogeneity in the patient population that is categorized as T3 laryngeal cancer. There is an acute need to re-evaluate treatment options for T3 laryngeal cancer. The authors would favour an individualized approach to the management of these patients and advise caution in advocating a primary non-surgical approach to all patients with this disease stage.

TREATMENT OPTIONS (TABLE 14.9)

Non-surgical treatment

Radiation therapy in combination with systemic therapy with either concurrent chemotherapy or Cetuximab (monoclonal antibody which competitively inhibits the cell-surface Epidermal Growth Factor Receptor-EGFR) or alone offers organ preservation in a proportion of appropriately selected patients without compromising survival. The landmark VA study[91] showed that in patients responding to induction chemotherapy, the laryngeal preservation rate was 64% at 2 years with similar survival rates at 2 years (68%) compared to surgery followed by RT. Salvage laryngectomy rates were significantly lower for T3 compared to T4 disease (29% vs 56%). A higher proportion of patients with glottic cancer (those with fixed cord) compared to supraglottic cancer underwent salvage laryngectomy.

A subsequent trial by the Intergroup RTOG 91-11[92] demonstrated that laryngeal preservation rates with concurrent chemoradiotherapy (CRT) was superior to sequential induction chemotherapy followed by RT and to RT alone (88% vs 75% vs 70%) with similar survival rates. The use of concurrent CRT in advanced laryngeal cancer is also supported by the tumour site specific meta-analysis and offers a 5.4% absolute benefit with the addition of chemotherapy at 5 years.[109] This benefit decreases with age and is non-significant above 70 years of age and therefore less appropriate in patients above this age. Combined modality treatment is associated with significant toxicities. The grade 3/4 toxicities related to treatment were 24% in ICT arm, 30% with CRT and 36% for RT arm with treatment related death of 3% in the ICT and RT arm and 5% in the CRT arm.[93] Robust data relating to laryngeal function preservation following CRT are lacking. The consensus panel now recommends the primary end point to be survival and function for future studies. A meaningful functional end point defined is laryngo-oesophageal dysfunction-free survival at 2 years.[105]

It must be emphasized that in the 91–11 trial the radiation therapy delivery was mostly unplanned or using 3D forward-planning technique whilst most centres now use the modern state of the art radiation therapy delivery intensity-modulated radiation therapy (IMRT) or volumetric modulated arc therapy (VMAT) which allows to conform the radiation doses to the target volume, minimize hot spots and spare dose to adjacent normal structures thereby potentially reduce the associated toxicities.

Standard concurrent chemotherapy regimens include cisplatin (100 mg/m^2) on day 1, 22 and 43 of RT and carboplatin/5 FU on weeks 1 and 5 during RT. In patients where chemotherapy is contraindicated, cetuximab, monoclonal antibody could be considered as an alternative in patients with performance status 0 or 1 during RT. The addition of cetuximab during RT has been shown to improve local control (3-year LRC 47% vs 34%) and 5-year overall survival by 10% (46% vs 36%) compared to RT alone (27% of patients are advanced laryngeal cancer).[111] The toxicities associated with cetuximab include acne form skin rash and hypersensitivity reactions and does not increase the rate of radiation induced mucosal toxicities.

Induction chemotherapy regimens include combination cisplatin and 5FU (PF) given every 3 weeks to a total of 2 to 3 cycles. This in selected patients may improve survival and reduce distant metastasis but its role is not proven prior to concurrent CRT. The addition of docetaxel to above drugs has shown a higher overall response rate and larynx preservation rate compared to PF in patients with stage III/IV laryngeal cancer and may improve survival.[111–115]

Standard fractionation RT alone may be used as a single modality treatment in patients over 70 years of age or where comorbidity precludes the use of concurrent chemotherapy or cetuximab. The outcomes are suboptimal compared to CRT and should only be considered in patients who are selected or chose to receive RT alone.

Altered fractionation regime improves local control and survival at the cost of higher mucosal toxicities but the outcomes are better than RT alone but are still suboptimal compared to concurrent CRT. Altered fractionation with hypoxic modifiers, namely nimorazole, is currently being studied in a UK clinical trial, NIMRAD (a randomized placebo-controlled trial of concurrent nimorazole vs RT alone in patients with locally advanced squamous cell carcinoma not suitable for concurrent chemotherapy or cetuximab).

The potential role of concurrent chemotherapy and dose-escalated RT in laryngeal and hypopharyngeal cancer has been studied in a phase III trial, ART DECO. The early results demonstrated no improvement in local control in the dose-escalated arm and an increased incidence of acute toxicities in the dose-escalated arm.

Primary non-surgical treatment with concurrent CRT remains the preferred treatment option in patients with the following: good performance status, minimal or no comorbidity, disease is limited to the confines of larynx with no cartilage invasion, functioning larynx with no airway compromise to achieve the best possible outcome of organ and function preservation.

Radiation Technique: Most centres in the UK and US routinely use IMRT for treatment (**Figure 14.5**). This allows the dose to be conformal around the target and minimize dose to the adjacent normal structures. This technique also allows the delivery of differential dose to the primary site, involved nodes and uninvolved at risk nodal levels simultaneously. Centres use either two- or three-dose levels for definitive treatment. The two-dose levels are 65-66 Gy for gross disease and 54 Gy for microscopic disease in 30 fractions. A dose of 60 Gy is used for regions at high risk of microscopic disease in centres where three dose levels are used.

In a node-negative patient, the nodal levels at risk for microscopic spread are bilateral level II to IVa and are treated to prophylactic dose of 54 Gy in 30 fractions. The levels are outlined using consensus guidelines.[116]

In a node-positive neck, in addition to level II to IVa, level Va, Vb are also at risk. In patients with level IIa involvement, level Ib and level VIIb (retrostyloid space) are at risk of microscopic spread and are treated to a prophylactic dose as above.

The management of residual neck nodes in patients with higher neck stage (N2b, N2c and N3) following CRT is guided by the results of PET scan done at 10–12 weeks post CRT. A salvage neck dissection is done in patients with positive or equivocal PET uptake.[117]

Open partial laryngectomy (OPL) and Transoral partial laryngectomy

As discussed above, several studies[47, 49, 97, 98] show comparable mature outcomes in patients with T3 cancer who received OPL or transoral partial laryngectomy as the primary management. In the systematic review by Thomas et al,[49] pooled local control rate at 24 months following primary open partial laryngectomy for 5061 patients; 832 patients had T3 or T4 cancers; despite this the LC and DFS rates were excellent. There will be an inevitable selection bias when these treatments are offered, and these are often single-centre series where pockets of expertise exist. A recent systematic review[104] of surgical and non-surgical organ preserving options showed that both OPL and TLM seem to be efficient organ preserving methods for the treatment of T3 squamous cell laryngeal cancer. However, comparisons between surgical and non-surgical treatments were not feasible in this study due to population heterogeneity; recognizing the above bias, some of the best organ preservation and survival rates and lowest recurrence rates were seen with OPL. The authors do not recommend organ preservation surgery for T3 cancers outside of a registered institutional protocol.

Total laryngectomy

Total laryngectomy is a bona fide treatment for T3 laryngeal disease, especially in patients who have laryngopharyngeal dysfunction or a fixed cord. For endolaryngeal tumours with no pathological evidence of neck disease, a total laryngectomy with adequate margins will be all that will be needed. These patients will not need reconstructive interventions as adequate pharynx will be available to create an adequately wide neopharynx.

T4 disease

There is general agreement that laryngeal cancer which extends outside the framework of the larynx should be treated by primary surgery.[118] The reasons for this consensus are that tumours invading the cartilage do not respond well to radiation, and even if tumour control is achieved, patients may be left with a non-functional larynx (poor airway with aspiration) and chondronecrosis, both of which will need surgery for management. There is also a high risk of gastrostomy dependence if this group of patients is treated with CRT.[119, 120] As discussed above, these hark back to the contraindications for organ preservation as discussed by the Larynx Preservation Consensus Panel (**Table 14.9**).

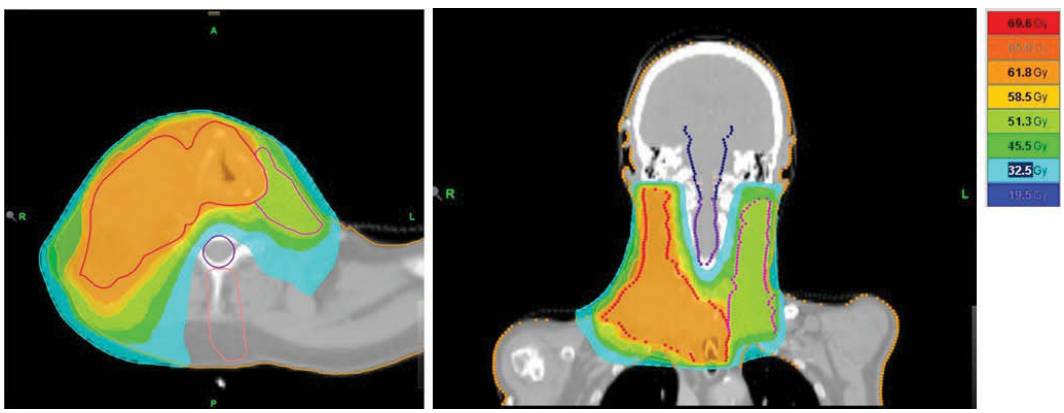


Figure 14.5 Axia and coronal section of an IMRT plan for a patient with T2N2b disease. The prescription dose (orange) encompasses entire larynx and involved nodal levels. The contra lateral at risk nodal level is treated with a prophylactic dose (green).

In an analysis of patients in the United States National Cancer Data Base diagnosed from 2004 to 2012 with T4N0 laryngeal cancer, Stokes et al. showed that overall survival among patients undergoing surgery with adjuvant radiation therapy (n = 1559) was superior to that of patients treated with concurrent CRT (n = 1597)[121] and single-centre reports support this position.[119]

Surgery usually takes the form of total laryngectomy, but for smaller selected tumours, open partial laryngectomy may be an option.[49] There are also reports supporting TLM resection for these tumours with good control rates,[122] but these have not been reproduced outside of experienced hands. Professional opinion on managing this disease is in favour of primary surgery followed by adjuvant therapy. Virtually all these patients will need the neck addressed based on the extent of neck disease; N0 necks will need bilateral levels II-IV neck dissection.

Adjuvant treatment

Post-operative RT to the tumour bed and/or neck in patients at risk of locoregional recurrence can improve locoregional control and survival. The risk factors are pT4 tumours, close or involved resection margins, involved node measuring more than 3 cm, multiple positive nodes and extracapsular spread. Other relative factors are perineural invasion and vascular invasion.

Concurrent chemotherapy and post-operative RT improves locoregional control and disease-free survival compared to post-operative RT in patients with risk factors for locoregional recurrences at the expense of increased mucosal and haematological toxicity. It improves overall survival in patients with positive resection margin and/or extracapsular spread and should be considered in patients with these risk factors for relapse.[123, 124]

TABLE 14.9 Recommended treatments for advanced laryngeal cancer

T stage	1st choice	2nd choice	3rd choice
T3	CRT	OPL/TLM/TORS*#	TL*#
T4a	TL#	CRT	OPL/TLM*#

* based on patient choice, local expertise, tumour and patient factors.
# may need adjuvant radiation based on pathological findings.

RECURRENT LARYNGEAL CANCER

Recurrent early laryngeal cancer

Residual or recurrent laryngeal cancer (hereafter referred to as recurrent cancer) following RT is a difficult clinical problem as the disease is more aggressive and carries a poor prognosis. Although several treatment options exist for patients with laryngeal cancer at first presentation, options for those with recurrent cancer will be limited based on the initial treatment received and the stage of the recurrent disease. Cancers that recur after radiation therapy often demonstrate aggressive behaviour, arise in a field where lymphatic drainage is unpredictable, and are associated with poor control rates. Salvage total laryngectomy (STL) is an often recommended option, even for early radiorecurrent cancers, because it is technically easy, and the outcomes are predictable.[124–126] Recognizing that recurrent head and neck squamous cell carcinoma has an aggressive course, and concerns about the higher incidence of complications in the irradiated neck, surgeons have been reluctant to adopt less radical procedures. However, total laryngectomy has far-reaching consequences for the patient in terms of function and quality of life.

OPL

OPL in recurrent cancer has withstood the test of time in instances where the tumour extent and patient are suitable for the procedure, and has been demonstrated to have very good outcomes in the recurrent setting too (**Figure 14.6**). Paleri et al.[128] performed a systematic review and a meta-analysis to study the role of open conservation (partial) laryngeal surgery in radiorecurrent laryngeal cancers. The pooled estimates of oncological outcomes were as follows: local control rate at 24 months for 560 patients was 86.9% (95% CI, 84%–89.5%), the disease-free survival rate for 352 patients was 91.2% (95% CI, 88.2%–93.9%), and the overall survival rate for 360 patients was 83.1%

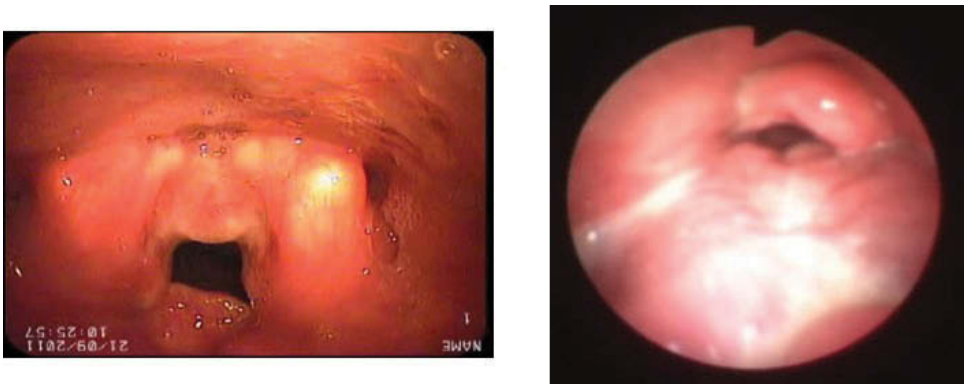


Figure 14.6 Two examples of salvage supracricoid laryngectomy. The patient on the left had both arytenoids and epiglottis preserved, while the one on the right had removal of epiglottis and the right arytenoid. In carefully selected patients and meticulous attention to operative detail, excellent function can be achieved.

(95% CI, 79.1%–86.7%). Since the review, further studies have demonstrated the efficacy of this approach in the radiorecurrent setting.[129]

TLM

As shown above, TLM has a well-defined and proven role in the management of primary laryngeal cancer with several advantages. It is therefore intuitive to try and exploit these advantages to early recurrent laryngeal cancer. However, there are several caveats to this approach. The conventional margins employed during TLM resection in the treatment of primary laryngeal cancer may well not be applicable in the radiorecurrent setting.[130] There is considerable difficulty in identifying peri-operative tumour margins accurately in a previously irradiated larynx, even in the most experienced hands. This is borne out by de Gier et al.[131] who reported a 58% recurrence rate after the first laser resection. Steiner et al.,[132] whose series included recurrent advanced tumours, reported only 38% remained free of disease after the first laser procedure. This improved to 71% following repeat TLM. Studies by Roedel et al.[133] and Ansarin et al.[134] revealed that recurrent tumour was typically clinically understaged and was later found to display a higher stage on pathological examination. This has also been demonstrated in other studies where whole organ sectioning has been employed, where pre-treatment clinical and radiological staging accuracy for recurrent tumour is around 50%, with more than 90% being understaged.[130] Ramakrishnan et al.[135] performed a systematic review of the use of salvage TLM and identified that although it was oncologically sound with a high larynx-preservation rate, there was a distinct trend towards inferior local control rates compared to OPL. The pooled mean estimate of local control at 24 months after first TLM (n = 249) was 56.9%, a full 30% less compared to the 24-month local control rates for OPL in recurrent cancers. This remained the case even when the improved LC following repeat TLM is taken into consideration. The relatively lower mean larynx preservation rate of 72.3% for TLM vs 84% for OPL[128] is a reflection of the higher locoregional failure following TLM and the lower threshold for resorting to a total laryngectomy. The authors believe that where suitable, patients should be offered OPL in preference to TLM for recurrent tumours, unless the cancer is limited to the mid cord and there is little concern about submucosal spread. In cases not suitable for OPL due to patient factors, total laryngectomy should be offered.

Recurrent advanced laryngeal cancer

Patients who recur following CRT are rarely candidates for anything less than a total laryngectomy. Recurrent T3 and T4 cancers with partial or limited erosion of the thyroid cartilage may be suitable for OPL, and there are data to support the oncological efficacy of this approach in carefully selected patients.[128]

Pharyngocutaneous fistulae (PCF) are known to occur in nearly a third of patients after STL.[127] PCF has severe impact on duration of admission and costs, quality of life and can even cause severe complications such as bleeding, infection and death. Paleri et al.[136] performed a meta-analysis of the benefit of vascularized tissue repair in reducing the risk of PCF following STL. Using data from 591 patients across 7 studies, the pooled incidence of PCF for 332 patients who underwent flap reconstruction was 22.2% (95% CI 17.9 to 26.8%), but 31.2% (95% CI 25.8 to 36.9%) in 259 patients who underwent primary closure. The absolute risk reduction in PCF rates of 9% indicates that 11 patients will need a flap to prevent one fistula. The pooled relative risk derived from 591 patients was 0.63 (95% CI: 0.47 to 0.85), indicating that patients who have flap reconstruction/reinforcement reduced their risk of PCF by a third. Another study by Sayles et al.[137] on the same subject, albeit with different inclusion criteria, published almost concurrently, arrived at similar conclusions. They concluded that relative risk of fistula was 0.57 (95% CI 0.37–0.85, $P < 0.001$) for STL with flap reinforced closure compared to primary closure of the pharynx alone and the number needed to treat to prevent one fistula was 6. These pooled analyses suggest that there is a clear advantage in using vascularized tissue from outside the radiation field in the laryngectomy defect (**Figure 14.7**).

Neck management in recurrent laryngeal cancer

A handful of studies have specifically looked at the utility of offering neck dissection to patients who present with recurrent laryngeal cancer.[138–145] Current imaging techniques to assess the post-treatment neck offer a high-negative predictive value (~96%) increasing clinical confidence. Given the increased complications associated with neck dissection in the salvage setting,[142] consideration should be given to conservative management of the neck

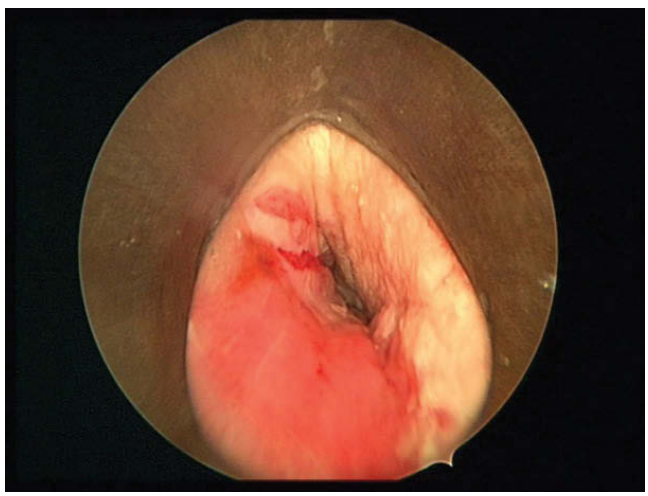


Figure 14.7 Endoscopic view of pharyngeal lumen augmented using a free cutaneous flap in a patient who underwent salvage laryngopharyngectomy.

in clinically node-negative patients, especially in patients who have received elective irradiation to the nodal basins. It should be noted that a similar philosophy has significant support in the post chemoradiated neck, where surgical salvage treatment is planned based on imaging findings. Following a comprehensive review of the question, Sanabria et al.[146] offered some recommendations on the subject. In patients with glottic tumours classified originally as early cancer (T1–2) and who recur with tumours of similar stages (rT1–2), an observation policy for the untreated neck is appropriate, if the imaging shows no neck disease. For recurrent early supraglottic cancers, it is very likely that the neck would have been previously treated and a neck dissection is not warranted if there is no clinical or radiological evidence of neck disease. For more advanced laryngeal tumour recurrences (rT3–4), the recommendation was for elective neck dissection (bilateral for supraglottic cancers), particularly if previous radiation fields did not include the lateral neck. It should be noted that if a free-flap reconstruction is to be performed for pharyngeal reinforcement or augmentation, limited dissection of at least one side of the neck may be necessary to site the microvascular anastamosis.

RARE CANCERS (SW)

While the majority of tumours of the larynx are squamous cell carcinomas a number of other pathologies can occur in the larynx. These include neuroendocrine, connective tissue, salivary gland, epithelial cell, malignant melanoma and immune cell derivatives. In a review of these in both the supraglottis and glottis the majority were in men in their 7th decade of life. In the supraglottis, neuroendocrine, small cell and lymphomas predominated. While in the glottis spindle cell, sarcomas and small cell tumours were more common. Limited data exist due to the relative rarity of these tumours to guide treatment.[147]

Neuroendocrine tumours are the most common non-squamous tumours of the larynx. Current consensus classifies them into paraganglioma, typical carcinoid tumour, atypical carcinoid tumour and small cell neuroendocrine carcinoma. Precise diagnosis is essential as natural history treatment and prognosis vary depending on the category. Surgery is the mainstay of treatment for typical and atypical carcinoid. Atypical carcinoid is considered more aggressive and therefore elective neck dissection is advocated, and adjuvant CRT should be considered. Paraganglioma is a benign entity and can typically be treated with surgery alone with an excellent prognosis. Small cell neuroendocrine carcinoma carries a poor prognosis (<5% 5-year survival) and surgery has been shown to offer no benefit when compared to CRT alone.[148]

Primary laryngeal lymphoma is extremely rare, and there is debate in the literature as to whether it constitutes an unusual presentation of non-Hodgkin lymphoma rather than being a separate disease entity. Treatment is targeted at the histological subtype of the lymphoma rather than the site at which it presents, and therefore surgery has a very limited role.

Laryngeal small-cell carcinoma is a subtype of the extrapulmonary small-cell carcinomas (EPSCC) carrying a generally poor prognosis when compared to pulmonary small cell carcinoma. EPSCC is usually a fatal disease, with a 13% 5-year survival rate. In a small percentage of patients, surgery can be curative if the tumour is small and confined to the organ of origin. Because of the poor overall outcome, one needs to consider the possible use of adjuvant chemotherapy in appropriate circumstances if surgery is to be employed. In most patients with limited disease, the combination of chemotherapy and radiation as the primary treatment can be as effective as surgery. EPSCC is responsive to commonly employed regimens for small-cell lung carcinoma; however, the responses are short-lived. The extent of disease at diagnosis represents the most sensitive predictor of survival.[149]

LARYNGEAL CANCER IN YOUNG AGE GROUPS

Laryngeal cancers in young people are much less common. In the US it is estimated that 26% of laryngeal cancers present under the age of 40.

There are a number of studies considering head and neck cancer in young adults, typically defined as younger than 45. In general, this age group has a lower proportion of alcohol drinkers and or smokers. For many subsites there appears to be an inverse relationship with fruit and vegetable intake.[150, 151] HPV infection may be more important in this age group, although epidemiological studies thus far have not shown a strong link as they have in oropharyngeal cancer.

A higher proportion are associated with genetic abnormalities, such as Fanconi's anaemia (FA), than in the older cohort. FA is a rare autosomal recessive inherited cancer syndrome is associated with defects in DNA repair. It is clinically characterized by congenital malformations, progressive bone marrow failure, and increased incidence of malignancies, especially acute myeloid leukemia and squamous cell carcinomas of the head and neck (HNSCCs). On a cellular level, typical features of the disorder are a high degree of genomic instability and an increased sensitivity to bi-functionally alkylating agents. Cisplatin-based chemotherapy, in combination with RT cannot be used in FA patients due to their propensity for increased toxicity. Surgery is the most important treatment option for HNSCC in FA patients, who also merit frequent screening for early detection of malignancies.[152]

Infection with the human immunodeficiency virus (HIV) has been positively linked with rare malignancies of the head and neck, such as Kaposi's sarcoma (KS), non-Hodgkin lymphoma, and more commonly squamous cell carcinoma. Head and neck involvement of KS is not unusual. However, laryngeal involvement is rare. Most patients have had AIDS-related KS, although HIV-negative persons with laryngeal KS have also been

noted. Of the AIDS cases reported, the majority (91%) were males of mean age 35 years (range 24–56 years), with advanced HIV disease, that were antiretroviral naïve. This may explain why many afflicted persons also had oropharyngeal, as well as cutaneous and visceral KS. Care should be taken when performing biopsy of these lesions as they are very vascular and can be associated with brisk, potentially fatal bleeding. Therapeutic options for this scenario include low-dose local irradiation, intralesional chemotherapy or laser ablation, and systemic therapy, particularly if there is disseminated KS. For laryngeal KS lesions producing acute or impending airway obstruction urgent intervention is necessary. However, depending on the location of the KS lesion, tracheostomy may contribute to mortality as a result of fatal haemorrhage. Therefore, cricothyroidotomy has been recommended by some authors as an alternative approach to life-threatening emergencies in this setting.[153]

It is rare to see these cancers in children (those under 18), however cases do occur, particularly in those with a genetic cause. Management will be multidisciplinary and should additionally involve the paediatric oncology teams. Treatment principles however are generally the same, and should be led by tumour histopathological type and subsite, as for adult patients.

KEY POINTS

- A binary grading system for laryngeal dysplasia is currently espoused.
- Management of laryngeal precancer is driven by consensus and logistics as high-level evidence is lacking.
- Transoral laser microsurgery is the preferred option for most T1a and some T1b lesions, based on clinical and cost-effectiveness analysis.
- For locally advanced tumours that have not caused laryngeal dysfunction, radiation therapy allows organ preservation, which is supported by high-level evidence.
- Good evidence exists to support local laryngectomy for T4a disease.
- Management of the neck should be based on the site and the stage of the primary tumour, the presence or absence of disease in the neck, with the treatment modality influenced by the treatment planned for the primary site.

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CHAPTER 15

REHABILITATION AFTER TOTAL LARYNGECTOMY

Yvonne Edels and Peter Clarke

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SEARCH STRATEGY

Data in this chapter may be updated by a PubMed search using the keywords: surgical voice restoration, laryngectomy and tracheo-oesophageal speech.

INTRODUCTION

Enormous advances in the treatment of cancer of the larynx have occurred since Theodor Billroth performed the first successful laryngectomy in Vienna in the year 1873.[1] Whilst removal of the malignancy and preservation of life remain the primary goal, attention is now directed at achieving functional outcomes for breathing, swallowing and speech to provide optimal quality of life. Management decisions are best made within designated head and neck units by the multidisciplinary team (MDT) of professionals who pool their individual specialist knowledge for the benefit of the patient. The weekly MDT meeting provides the forum for discussion of cases allowing all members to contribute to patient management.[2] Core MDT members include the surgeon, clinical oncologist, pathologist, plastic surgeon, staff nurse, dietician, speech and language therapist (SLT), clinical nurse specialist (CNS), physiotherapist and psychologist.

BACKGROUND

In the presence of advanced disease or recurrence following initial treatment with radiotherapy or chemoradiotherapy, total laryngectomy is often the only available treatment option, with the intent to remove the entire larynx and the cancer. This is major life-changing surgery and the news is almost never welcome. Patients and their close relatives need time and the opportunity to ask questions, and should be offered counselling to understand the considerable implications of a total laryngectomy;[3] these include the formation of a permanent neck stoma, changes to breathing, swallowing and of course the loss of the vocal cords and normal voice production (**Figures 15.1** and **15.2**). This role generally falls to the SLT, the CNS or both. It can take repeated explanations aided by information sheets, diagrams, photos and videos before patients absorb the information. They should be offered the opportunity to also meet other carefully selected laryngectomies. Hence, the rehabilitation starts prior to surgery and enables patients to have realistic expectations.

In addition to the above, counselling should also include detailed information about the various options for voice production. These are oesophageal speech, the artificial larynx and surgical voice restoration (SVR). The latter involves the creation of a tracheo-oesophageal puncture (TEP) at the time of primary surgery or at a later date. The TEP is a fistula through the posterior tracheal wall into the oesophagus. This TEP is stented open with a Foley catheter or a one-way valve made of medical grade silicone. Air can pass into the oesophagus for voice production when the stomal exit is temporarily covered, but food and fluid are not aspirated (**Figure 15.3**).

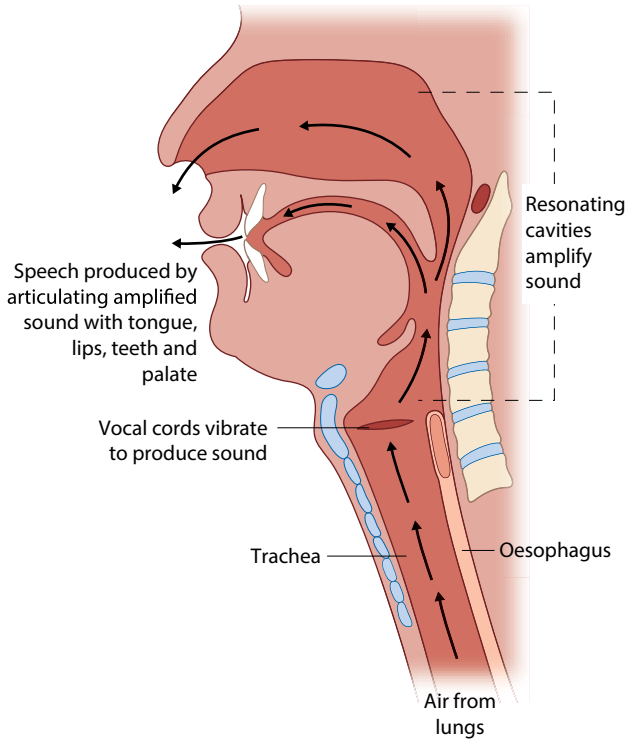


Figure 15.1 Laryngeal voice production.

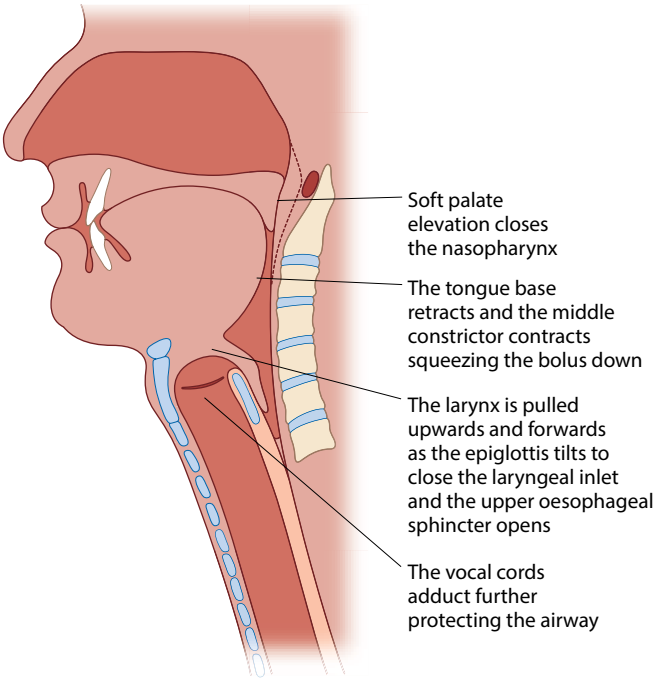


Figure 15.2 Normal laryngeal swallow.

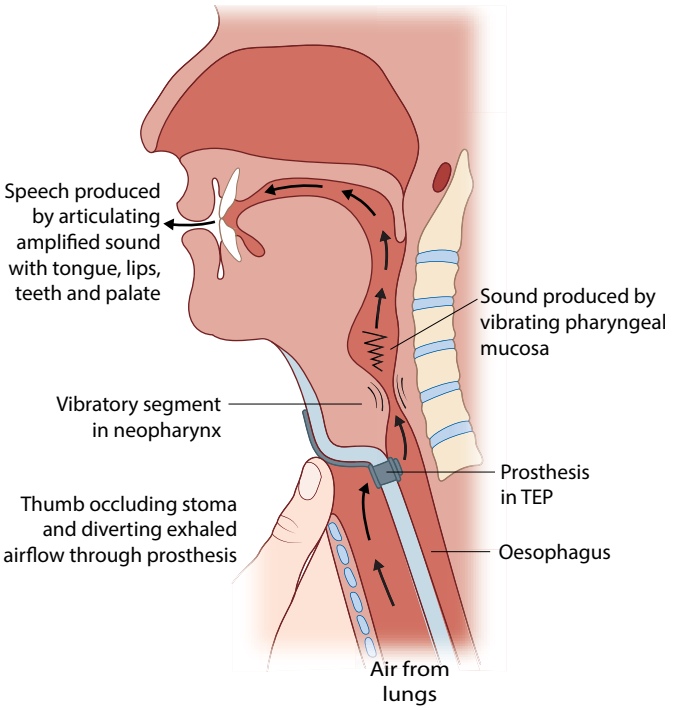


Figure 15.3 Surgical voice production.

SURGICAL TECHNIQUE TO OPTIMIZE SPEECH AND SWALLOW

Tumour resection

Of prime importance is the need to resect all diseased tissue to provide good oncological results. There are, however, a number of fundamental steps that improve the voice and swallowing results and these should be undertaken if they do not compromise the oncological resection.

The laryngectomy is carried out in the usual fashion conserving as much pharyngeal mucosa as possible, particularly over the postcricoid region, the piriform fossae and the valleculae, provided safe clearance from the tumour is obtained. The thyropharyngeus and cricopharyngeus muscles should be dissected off the thyroid laminae on both sides preserving as much muscle as possible (**Figure 15.4**). For hypopharyngeal tumours the mucosa of the uninvolved piriform fossa is carefully preserved to minimize the need for flap reconstruction. Ideally a transverse, unstretched mucosal width of at least 6 cm at the narrowest point is necessary to enable adequate swallowing and effortless tracheo-oesophageal speech. Augmentation of the pharynx with a flap is preferable if the residual mucosal strip is less than 6 cm to avoid pharyngeal stenosis and functional impairment. Irrespective of the available mucosal width, vascularized tissue reconstruction is preferred in the setting of the salvage laryngectomy after chemoradiotherapy, as this strategy reduces the risk of pharyngocutaneous fistula formation by a third.[4]

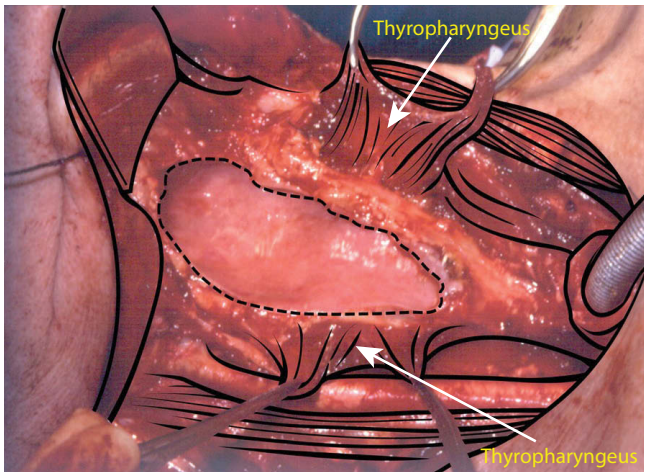


Figure 15.4 Preservation of thyropharyngeus for later muscle repair.

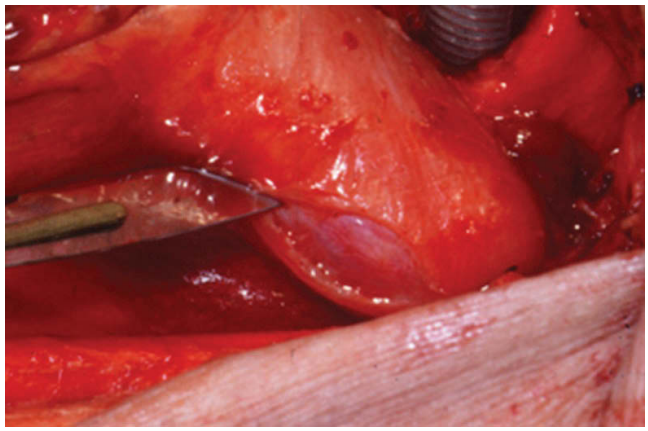


Figure 15.5 Myotomy through upper oesophageal muscles to underlying mucosa.

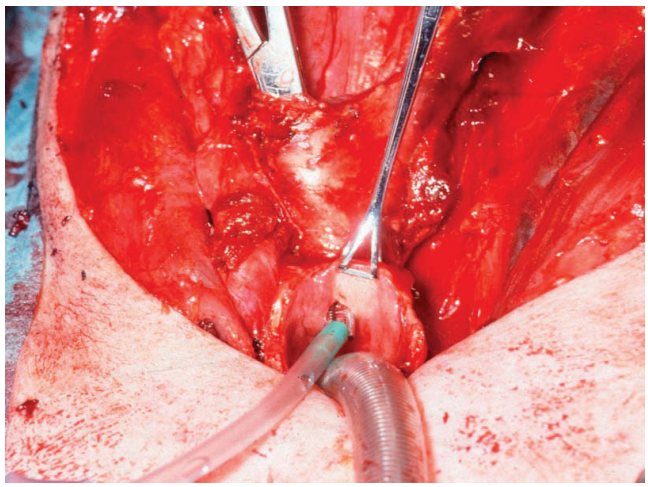


Figure 15.6 Tracheo-oesophageal puncture.

Cricopharyngeal myotomy

Once the larynx is removed, a myotomy of the upper oesophageal sphincter is carried out. This is important to avoid hypertonicity and spasm of these muscles during attempted phonation, and to allow expansion of the upper oesophagus providing an air 'reservoir' below the pharyngo-oesophageal (PE) segment. Hypertonicity or spasm will interrupt the flow of air to a varying degree, restricting or completely stopping voice production. This spasm appears to be caused by reflex contraction of cricopharyngeal and constrictor muscles when the upper oesophagus is distended with air, and is a cause of TEP speech failure in 10–12% of patients.

A short posterior midline myotomy is carried out with a scalpel over a distance of 4–5 cm starting from just below the level of the TEP site, extending cranially into the fibres of the thyropharyngeus. This divides the circular muscle fibres in the upper oesophagus and the cricopharyngeus. It is important that all muscle fibres are cut (**Figure 15.5**). It is unclear whether assessment of the upper oesophageal sphincter with a finger can predict the development of spasm and there seems little contraindication to doing a myotomy on all patients as it may also improve swallow. One of the conclusions of the European multicentre audit of speech and swallowing results after laryngectomy was that myotomy improved voice outcomes.

A unilateral pharyngeal plexus neurectomy has been advocated in the past as an alternative method of constrictor relaxation. Three to five branches of the plexus entering the lateral wall of the pharynx are exposed and identified with a nerve stimulator before division with cautery. This technique has not gained widespread use.

Tracheo-oesophageal puncture

The puncture is positioned in the midline about 10–15 mm below the cut edge of posterior tracheal wall. The tip of a pair of curved artery forceps is inserted through the pharyngeal defect and advanced into the upper oesophagus just as far as the puncture site, tenting up the mucosa. A scalpel is used to incise minimally and horizontally through the mucosa and muscle onto the tip of the forceps, which are then advanced into the tracheal lumen and opened to grasp the tip of a 14 NG tube or Foley catheter (**Figure 15.6**). The forceps and the catheter are then withdrawn through the fistula tract and the tip of the catheter is passed distally down the oesophagus. The catheter is anchored to the skin above the stoma at the end of the procedure. Absorbable sutures between the oesophageal wall and the posterior aspect of the trachealis on either side of the proposed position of the puncture secures the party wall and avoids inadvertent separation. An alternative technique is to insert a valve at the time of surgery through the newly created puncture.

Pharyngeal closure

The pharyngeal defect can be closed using an interrupted or continuous absorbable mucosal suture; A horizontal closure is considered to produce a wider pharynx above

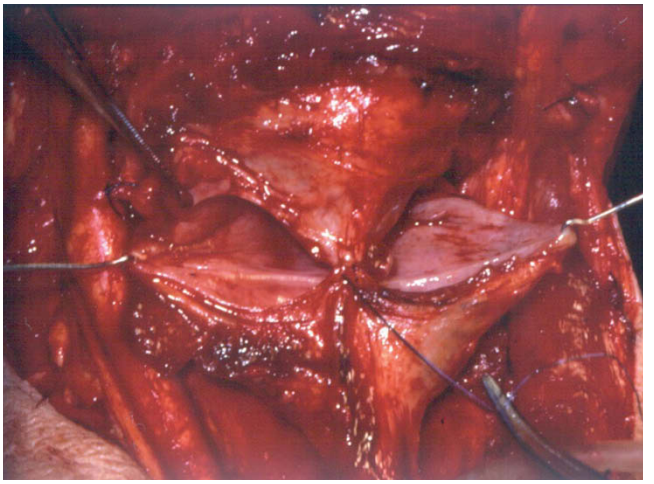


Figure 15.7 Horizontal pharyngeal closure.

the PE segment and may improve resonance for speech (**Figure 15.7**).[5] An alternative technique is the 'T' closure.

Based on how much constrictor muscle is available, an interrupted closure of the muscle is appropriate It is hypothesized that the constrictor muscle closure creates a suitable, 'tonic' PE segment at the optimal site in the pharynx with a good reservoir below it and a wide resonating pharyngeal segment above.[6] Whilst the upper oesophagus needs to be relaxed so that it does not respond to air being injected through the valve by going into spasm, the neopharynx or PE segment needs to provide an area where the mucosa is in apposition to allow it to vibrate efficiently and produce strong voice. Repairing the thyropharyngeus provides this vibratory segment. Conversely, if the muscles or PE segment wall are hypotonic (e.g. after total pharyngolaryngectomy and reconstruction or if thyropharyngeus is not repaired) the voice will be weak because there is minimal or absent muscle in the wall to create a PE segment. However, others[7] have recommended 'half-muscle closure technique', where only one side of the remnant constrictor muscles is used to reinforce the primary closure, with the advantage of reducing pharyngoesophageal spasm. Significant resection of the hypopharynx will necessitate a flap reconstruction.

Repair of the suprahyoid muscles

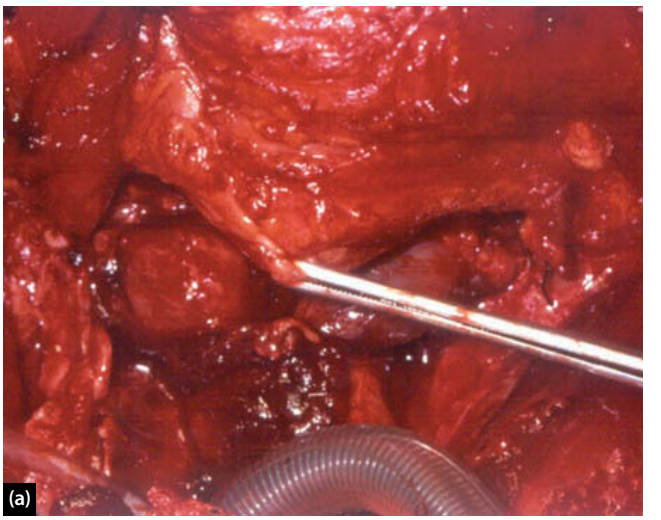
Following repair of the thyropharyngeus it is important to suture the suprahyoid muscles down to the thryopharyngeus. This strengthens the mucosa above the repair, so avoiding a pseudoepiglottis and anterior pouch that may affect swallow, and also reattaches the middle constrictor and other suprahyoid muscles which are important in the swallow reflex (**Figure 15.8**).[8]

Stoma reconstruction

The size, shape and contour of the stoma and surrounding skin are important to aid digital occlusion of the stoma and help ensure optimal adhesion of the base plate for the tracheostoma valve housing. In order to avoid unnecessary tracheal retraction, care should be taken during the laryngectomy not to transect the trachea too low; if necessary, the margins of the trachea can be sutured to the medial margins of the sternomastoid muscle to secure it near the skin. If the tendons of the sternomastoid muscle are prominent, they can be safely divided to ensure a flatter area around the stoma for better base plate adhesion.

Post-operative care

Post-operatively the patient must be fed enterally either naso-gastrically or via a catheter placed through the TEP or the prosthesis, and then directed into the stomach. After an appropriate healing period, which may be significantly longer after chemoradiotherapy, oral feeding is reintroduced, beginning with water and quickly building



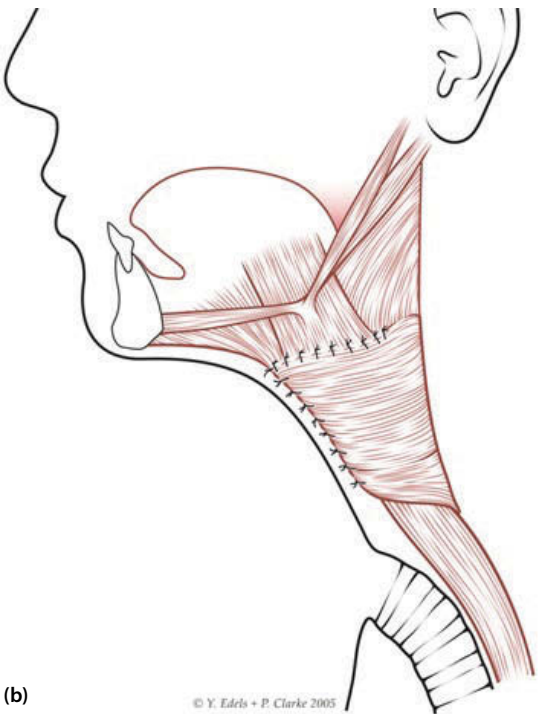


Figure 15.8 Closure of the suprahyoid muscles.

to pureed food, soft food and ultimately a normal diet. Work on voice production begins when adequate healing has taken place. If phonation begins too early, excess pressure during voicing can lead to suture line breakdown.[9] Patients not yet fitted with a voice prosthesis must be sized and fitted at this point. There is increasing support for early feeding, commencing as early as the second post-operative day in patients who have undergone laryngectomy as the primary treatment, as there is no good evidence that this increases the risk of pharyngocutaneous fistula formation.[10]

SECONDARY VOICE RESTORATION

The technique of TEP with prosthetic valve and voice restoration was originally developed for those patients who had failed to achieve adequate oesophageal speech. However, present day indications are mainly for patients who have complex resections and reconstructions, or those undergoing salvage surgery.

Laryngectomies need a tonic PE segment to provide a satisfactory vibratory source for tracheo-oesophageal speech. The first step in assessing patients who present for secondary voice restoration after laryngectomy, when they have failed oesophageal speech acquisition, should be an assessment of PE segment tonicity. A preliminary videofluoroscopy will determine whether it is necessary to inject botulinum toxin into the cricopharyngeus. If the end tracheostoma is too narrow for valve maintenance, a stoma revision may also be indicated at the time of the TEP. The patient should be judged to have adequate lung function to open the valve and produce voice.

Timing of valve placement varies, with the choices being placement of a sterile prosthesis either during surgery or post-operatively once healing has occurred. Either way, the length of the TEP must be carefully measured with a sizing gauge and the overall form and function of the site assessed before selecting an appropriate prosthesis from the extensive range available. One size does not fit all; thus the Blom-Singer and Provox prostheses range include valves of different diameters, lengths, opening pressures and design as well as custom-made varieties, so rarely is it not possible to find an appropriate one. Ex-dwelling prostheses can be self-changed by the patient or carer, freeing the patient from regular hospital attendance, while indwelling prostheses are to be changed by the healthcare professional only, and can remain *in situ* over extended periods.

HEAT AND MOISTURE EXCHANGE

Essential areas for rehabilitation include respiration, swallowing and voice production. Nasal functions of air humidification, filtration and warming are lost when air is taken in via the stoma.[11] The loss of the height from nose to stoma reduces air resistance within the lungs leading to less optimal gaseous exchange. A heat and moisture exchanger (HME), works as an artificial nose, reducing mucus over-production due to loss of nasal humidification, warming and filtering the air thus reducing coughing and assisting sleep. The HME consists of a small filter contained in a cassette, attached in front of the stoma either by a base plate stuck to the parastomal skin or inserted into a laryngectomy tube. Different designs exist, with specifications for daily activity, sleep and exercise. Ideally, an HME should be provided within a few days of surgery to minimize the risk of becoming accustomed to the reduction in respiratory pressure, which can be difficult to re-educate later. Failure to use an HME is mostly related to getting it to attach and remain attached. Difficulties may be due to post-treatment effects on the neck tissue or because the sternocleidomastoid muscles were not divided at laryngectomy to provide a flattened parastomal area for successful attachment. The increased need for pedicled or free flap reconstruction of laryngectomy defects after chemoradiotherapy also distort the anatomy around the stoma making the use of standard base plates difficult. Products exist to clean, moisturize and assist with better base plate attachment, often after a certain amount of trial and error. Several randomized studies have shown clear benefit from HME use in reducing pulmonary symptoms and improving lung function.[12, 13]

SWALLOW

Removal of the hyoid bone and larynx during laryngectomy and separation of the trachea and oesophagus into discrete systems destroys the normal sequential muscular swallow sequence. All laryngectomies have a modified swallow, and the differences between laryngeal and alaryngeal swallow are identified in **Table 15.1**. The key aspects of pharyngeal reconstruction that contribute to a good swallow are discussed above.

SPEECH

Oesophageal speech requires air to be taken into the top of the oesophagus either by injection or inhalation,[14] and then forced out again causing the newly reconstructed pharynx, the PE or vibratory segment, to vibrate in response to the flow of air and produce sound. As in normal laryngeal voice production, this sound is amplified by the resonating cavities above and modified into speech by the articulators, tongue, teeth, lips and soft palate. The electrolarynx produces a sound that is then transmitted into the resonating cavities either by direct pressure of the machine against the skin of the upper neck or through a tube directly into the oral cavity. SVR has largely replaced these other methods, being easier to learn and producing better quality voice (**Table 15.2**).

SVR voice is produced when the stoma is temporarily sealed by a finger placed in front of it or over the HME cassette. Later, the patient may use an adjustable tracheostoma valve (ATSV) allowing hands free speech (**Figure 15.9**). The ATSV seals when the expiratory breath

TABLE 15.1 Differences between laryngeal and alaryngeal swallow

	Oral	Pharyngeal	Laryngeal	Top of oesophagus	Oesophagus
Laryngeal swallow	Lips seal. Teeth, tongue, hard and soft palate form bolus and pass it to the back of the mouth	Soft palate elevates to close nasal port. Back/base of tongue and posterior pharyngeal wall close together. Stripping action propels bolus onward. Swallow sequence fires	Suprahyoid's contract, elevating and tilting larynx forwards and tucking it under the tongue. This action also pulls on the cricopharyngeal muscles helping them to relax and open the top of the oesophagus. The epiglottis biomechanically tilts over, sealing the tracheal entrance and the laryngeal sphincters close together to protect the airway.	Oesophageal entrance opens. Negative pressure created as oesophagus widens helps to draw the bolus in. The bolus enters the oesophagus.	Gravity and the sequential peristaltic wave carry the bolus to the stomach. Lower oesophageal sphincter relaxes and opens to allow bolus to pass.
Alaryngeal swallow	Lips seal. Teeth, tongue, hard and soft palate form bolus and pass it to the back of the mouth.	Soft palate elevates. Tongue back/base approximates posterior pharyngeal wall. Partial/reduced stripping action of posterior pharyngeal wall due to surgery and denervation. Bolus transits pharynx under gravity and power created here. Swallow sequence follows.	Reattached suprahyoids contract, pulling on the top edge of the reconstructed thyropharyngeus muscles and possibly also helping to lift the reconstructed pharynx. Reconstructed thyropharyngeus (and possibly cricopharyngeus) are stretched and relax, helping to open the entrance to the oesophagus. Bolus, under reduced pressure from tongue base/posterior pharyngeal wall contraction, exerts pressure from above. Reduced stripping action together with gravity move bolus on.	Oesophageal entrance opens. Bolus under pressure from above and gravity enters the oesophagus.	Gravity and the sequential peristaltic wave carry the bolus to the stomach. Lower oesophageal sphincter relaxes and opens to allow bolus to pass.

TABLE 15.2 Comparison of speech production before and after laryngectomy

Physical requirements	Normal laryngeal voice production	Oesophageal speech production	Surgical voice production
Initiator	Moving column of air from the lungs	Moving column of air from the oesophagus	Moving column of air from the lungs
Vibrator	Vocal cords	Vibratory/pharyngo-oesophageal (PE) segment	Vibratory/pharyngo-oesophageal (PE) segment
Resonators	Resonating cavities: nose, mouth, pharynx	Resonating cavities: nose, mouth, pharynx	Resonating cavities: nose, mouth pharynx

is strong enough to close its valve and remains shut as long as this pressure is maintained. Once the air pressure falls the ATSV reopens and a new breath is taken in. Regardless of method, once the stoma is sealed, air passes via the voice prosthesis into the oesophagus making the walls of the vibratory segment (i.e. the area between the top of the oesophagus and the base of the pharynx) vibrate to produce sound. This basic tone is again amplified by the resonating cavities above (pharynx, nose and mouth) and modified into speech by the articulators. Outcome measures for post-laryngectomy speechg are evaluated by Deore et al.[15]

TONICITY

For optimal outcomes, the newly created reconstructed/vibratory segment must dilate on swallow and vibrate for voice. This area must be surrounded by tonic muscles to produce optimum voice.[16] If the neopharynx is too loose (hypotonic), the swallow is functional but voice quality is low, weak, whispery and often wet; if it is too tight (hypertonic), swallowing requires increased pressure and the voice is high pitched, effortful and difficult or impossible to maintain.

Hypotonicity is managed using digital pressure against the outside of the neck, artificially increasing the tone. Less severe hypertonicity is managed with a low opening pressure prosthesis but when insufficient, other measures must be considered.

Stretch receptors located within the muscles at the top of the oesophagus respond to being dilated by clamping down, preventing the free passage of air for voice production.[6, 17] By interfering with this mechanism hypertonicity and spasm can be avoided. This is effectively managed at the time of surgery by performing a myotomy[18–20] or neurectomy.[21] A myotomy should cut through all the muscles in the lower third of the reconstructed segment extending down to the level of the puncture (**Figure 15.10**). The upper two-thirds of the vibratory segment is spared leaving these muscles tonic for good voice production.

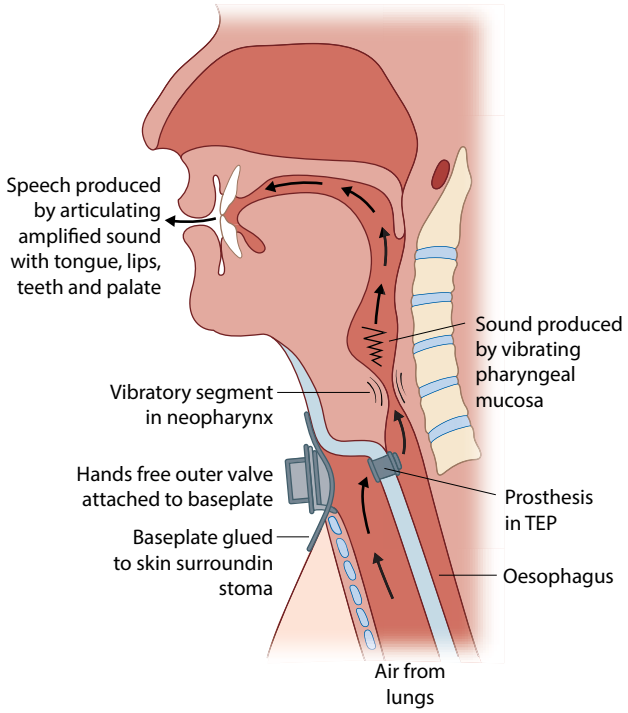


Figure 15.9 Hands-free surgical voice production.

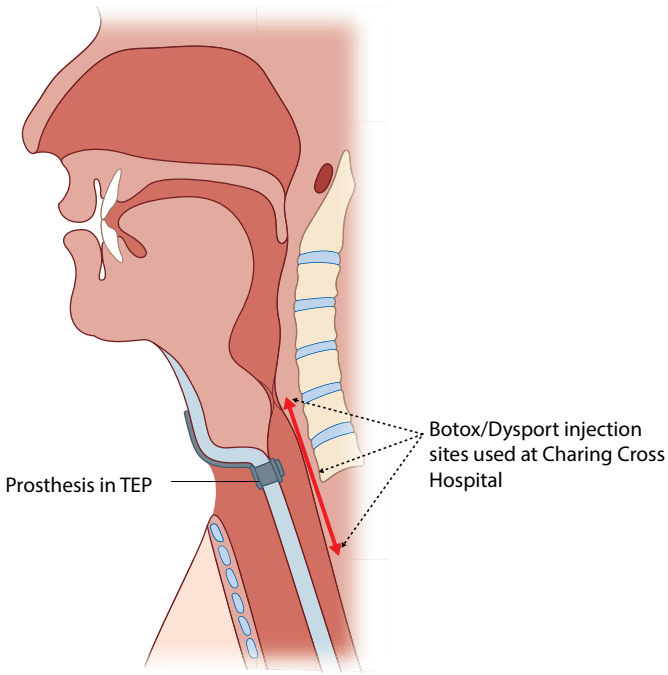


Figure 15.10 The myotomy is made posteriorly from the level of the cricopharyngeus down to below the level of the tracheo-oesophageal puncture. Botox/Dysport injection sites used at Charing Cross Hospital.

Hypertonicity/spasm that develops post-operatively can be managed with an open myotomy or chemical neurectomy. Since the introduction of botulinum toxin,[22] myotomy involving reopening the neck and dividing all the muscles including those of the reconstructed/vibratory segment is rarely performed, as it may cause hypotonicity and involves the risk of perforation.

A full videofluoroscopic assessment of swallow and voice should be carried out followed by a lignocaine injection to confirm the diagnosis.[23] Botulinum toxin is injected unilaterally at three sites along the same short myotomy line (**Figure 15.10**). The dosage administered is influenced by the degree of hypertonicity, neck fibrosis and stricture, whether a primary myotomy was performed and the surgical reconstruction. Injection of botulinum toxin can be repeated, though a single treatment is often sufficient to allow continued tonic voice.

PROBLEM-SOLVING

Problems occur both with the TEP and prosthesis.

Candida albicans

Candida spp. thrive in warm moist environments with a pH near 6.5 (e.g. oesophagus).[24, 25] A voice prosthesis acts as a foreign body within the TEP, becoming covered by a biofilm of bacteria and yeasts, forming plaques (**Figure 15.11**). *Candida albicans* interferes with the prosthesis valve mechanism, causing leakage and aspiration or increasing airflow resistance such that the prosthesis becomes non-functional.[24, 26–28] *Candida* spp. can also develop on the outside of the prosthesis burrowing into local tissue and causing an allergic type reaction (granulation tissue; see 'Granulation' below) (**Figure 15.12**).[24]

Figure 15.11 New prosthesis and one covered in a biofilm bacteria and yeats.

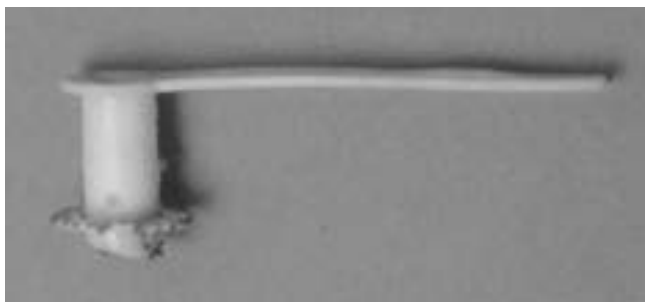


Figure 15.12 Candida species adherent to prosthesis.

Patients should brush and flush their prosthesis daily *in situ*,[29] possibly including a liquid antifungal (e.g. nystatin).[30] Exdwelling prostheses should be regularly removed, washed and sterilized overnight in 3% hydrogen peroxide.[31] If the estimated prosthesis lifetime[32] is too short, the prosthesis should be sent for mycological analysis and the results will indicate the appropriate antifungal to prescribe. Prostheses impregnated with antifungals are available at a cost. Fungal resistant materials are being developed;[33] meanwhile, dietary adjustment including the addition of probiotics should be considered.[34–36]

Granulation

Granulation is connective tissue thought to occur as an acute inflammatory response to a complex interaction between the prosthesis, *Candida* spp and the patient's tissue.[24] Removal of the voice prosthesis can cause bleeding and the open wound acts as a source for further infection. Small areas can be cauterized using a silver nitrate stick but larger areas require surgical removal (**Figures 15.13** and **15.14**). Prosthesis function may be disturbed and lead to TEP closure. Managing the *Candida* colonization is essential to prevent it recurring.

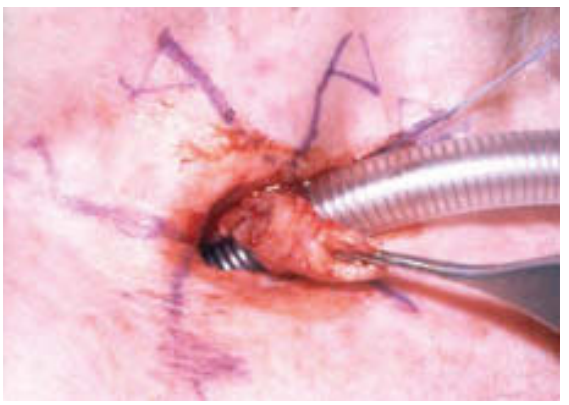


Figure 15.13 Excess granulation tissue being removed from tracheo-oesophageal puncture site.

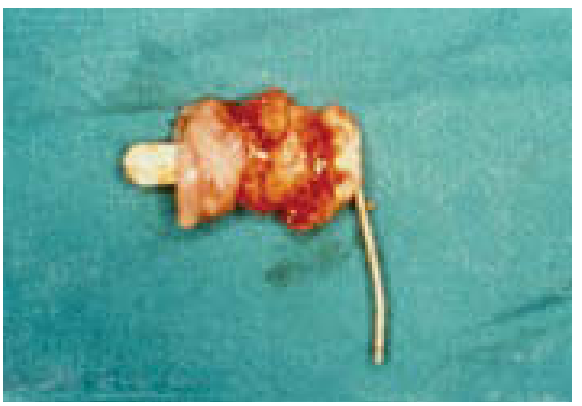


Figure 15.14 Granulation tissue removed from around prosthesis.

Reflux

Reflux causes oesophagitis and heartburn, and encourages *Candida* spp growth, granulation tissue formation and TEP dilation.[25] Its influence has been under-recognized.[25] Management of reflux is discussed in detail in Chapter 77, Reflux disease.

Central leakage

Candida interfering with prosthesis valving function is the most common cause of prosthesis central leakage.[27] This results in aspiration and increases the risk of chest infections. Other causes include prosthesis fouling against the posterior oesophageal wall while swallowing or negative pressure created within the oesophagus leading to inappropriate valve opening. Alternative prostheses with more appropriate sizes should be selected.

Peripheral leakage

This happens when the tissue around the TEP no longer beds down snugly onto the prosthesis barrel and allows saliva or liquid to penetrate around the prosthesis and hence aspirated into the trachea causing coughing or chest infections. Peripheral leakages should be managed prophylactically, anticipating and preventing this problem.

Reported reasons for peripheral leakage include:

- an oversized prosthesis pistoning within the TEP, suctioning the bolus through[31]
- a thinned or weakened party wall (below 8 mm), associated with a wider diameter prosthesis *in situ*[37, 38] often in patients with concurrent comorbidity (e.g. diabetes).[39]

Prevention can be achieved by the following measures:

- minimizing trauma by avoiding dilation of the TEP[37] and reducing the number of changes
- when changing the prosthesis, one option is to cut the *in situ* prosthesis in half, removing the anterior portion and allowing the posterior portion to pass out through the patient[40]
- hand-load the prosthesis into a smaller gel cap for placement.

Additional options include:

- injecting a filler to bulk the party wall[39, 41]
- using successively smaller diameter catheters to shrink the TEP (e.g. from a 20 FG to 16 FG)[42]
- using a snugly fitting extended flange prosthesis to cover the gap (**Figure 15.15**)[39]
- purse string suture procedures, reported to have poor success rates.[43]

Figure 15.15 Extended flange prosthesis and pushing device to help placement into the gelcap.

KEY POINTS

- Management decisions about rehabilitation after laryngectomy should be made within dedicated head and neck units by the multidisciplinary team.
- Surgical voice restoration should be offered to patients undergoing laryngectomy.
- Attention to surgical detail and long-term speech and language therapist input is required to optimize speech and swallowing after laryngectomy.
- Patients should commence wearing heat and moisture exchange devices as soon as possible after laryngectomy.

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CHAPTER 16

MANAGEMENT OF HYPOPHARYNGEAL CANCER

Prathamesh S. Pai, Deepa Nair, Sarbani Ghosh Laskar and Kumar Prabhash

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SEARCH STRATEGY

A search of PubMed with MeSH headings hypopharynx, piriform fossa, postcricoid,posterior pharyngeal wall, tumour, cancer, squamous cell carcinoma, gastric pull up, free jejunal graft, radiotherapy, chemotherapy,Trans Oral Videoendoscopic Surgery,Transoral Laser surgery, pharyngectomy, laryngopharyngectomy, near total laryngectomy in various combinations was carried out.

INTRODUCTION

Hypopharynx is the caudal part of the pharynx, also called laryngopharynx, extending from the hyoid bone to the lower margin of the cricoid cartilage. It is a dynamic conduit between the oropharynx and oesophagus and has three subsites – pyriform sinus, post-cricoid area and posterior pharyngeal wall. Laryngeal and hypopharyngeal cancers are often clubbed together due to their anatomic proximity. However, hypopharyngeal cancers are distinctly different from laryngeal cancers in terms of presentation, management and prognosis.

EPIDEMIOLOGY

Hypopharyngeal cancers are rare, and account for less than 0.5% of all cancers and 3–5% of head and neck cancers.[1–3] They have a large geographical variation, being relatively rare in Eastern Asia, Africa and Northern Europe (incidence under 0.5:100,000) and more common in India, Brazil, Central and Western Europe (incidence of 2.5:100,000). The incidence in India and France are substantially higher at 8–15 cases per 100,000 population in males.[4]

Hypopharyngeal cancers occur in individuals above 50 years of age, with a peak incidence in the sixth and seventh decades.[5] The most common site of origin is the pyriform sinus followed by the posterior pharyngeal wall and the postcricoid area. Pyriform and posterior pharyngeal wall lesions are more common in males, whereas postcricoid cancers are predominant in females.[6–9] The most common histology at this site is squamous cell carcinoma.

SURGICAL ANATOMY

The hypopharynx lies below and behind the base of tongue and larynx. It extends from the level of the hyoid bone to the lower border of the cricoid cartilage. It is comprised of three subsites: pyriform sinus, postcricoid area and posterior pharyngeal wall.

The pyriform sinus is a funnel-shaped lateral channel on either side of the larynx beginning at the level of the pharyngoepiglottic fold. It has a lateral wall which is contiguous with the posterior pharyngeal wall, a medial wall that forms part of the aryepiglottic fold converging into the postcricoid mucosa medially, and opens posteriorly into the lumen of the pharynx.

The pyriform sinus is bound laterally by the thyrohyoid membrane and medially by the aryepiglottic fold. The tumours tend to spread through this membrane beyond the larynx without cartilage destruction, keeping the laryngeal function somewhat intact. This is relevant in treatment planning.

The pyriform apex lies at the junction of the medial and lateral walls, deep and inferior within the pyriform sinus. It is related laterally to the thyroid cartilage, medially to the cricoid cartilage and lies inferior to the paraglottic space. Tumours involving the pyriform apex can easily spread superiorly into the paraglottic area causing vocal cord fixity. Tumours of the pyriform apex are in close proximity to the cricoid cartilage and oncological removal necessitates removal of the cricoid cartilage. This has implications when considering conservation laryngeal surgery. Tumours from the pyriform apex can also escape via the cricothyroid membrane early on beyond the laryngeal framework and need careful evaluation.

The postcricoid area lies behind the larynx and is located below the level of the arytenoid cartilages and extends to the inferior border of the cricoid cartilage. It continues below into the cricopharynx which lies at the upper end of oesophagus. Tumours in this region often involve the cricoarytenoid joints causing vocal cord fixity and/or aspiration. Being a junctional region, obstruction to the passage of food occurs early on and tumours often extend into the oesophagus inferiorly, mandating evaluation of the lower extent of tumour spread.

The posterior pharyngeal wall is the part of the hypopharynx between the lateral walls of the pyriform sinuses extend from the hyoid above to the level of the arytenoids below. It is separated from the prevertebral muscles by the prevertebral fascia. Tumours in this region can spread in either direction and even involve the prevertebral fascia and muscles early on in their spread.

The wall of the hypopharynx consists of four layers – 1) lining formed by non-keratinized stratified squamous epithelium; 2) pharyngobasilar fascia; 3) muscular layer formed by the lower fibres of the middle constrictor and the inferior constrictor muscles and 4) buccopharyngeal fascia. The hypopharynx derives its major blood supply from the superior thyroid arteries along with collaterals from the lingual and ascending pharyngeal vessels. Care should be taken not to devascularize the remnant pharynx during surgery to avoid pharyngocutaneous fistulae. Motor and sensory supply is provided by the pharyngeal plexus, formed by branches of the glossopharyngeal and vagus nerves. The vagus nerve via Arnolds nerve provides sensory innervation of the external auditory canal and is responsible for referred otalgia in hypopharyngeal cancers. Further description of the hypopharyngeal anatomy can be seen in Chapter 58, Anatomy of the larynx and tracheobronchial tree.

The hypopharynx has a rich lymphatic drainage (**Figure 16.1**). The pyriform sinuses drain to the deep cervical chain – the jugulodigastric and jugulo-omohyoid nodes. The pyriform sinus apex as well as postcricoid area drain into the paratracheal nodes while the posterior pharyngeal wall drains into the retropharyngeal nodes.[10] Careful evaluation of the tumour location and its draining lymph nodes is important in treatment planning in context of lymph node dissection and radiation therapy planning (**Figure 16.1**).

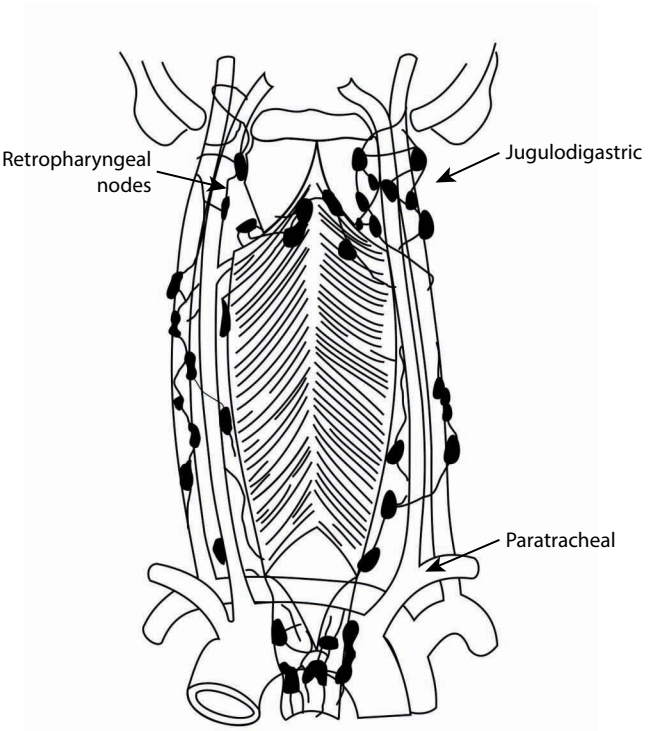

Figure 16.1 Lymphatic drainage of the hypopharynx.

AETIOLOGY

Hypopharyngeal cancers have multifactorial aetiology, predominantly associated with tobacco and alcohol usage. Air-cured tobacco is associated with a higher risk than the flue-cured one of developing laryngo-pharyngeal cancer.[11] Current smokers have a 8.53 higher incidence rate as compared to never smokers.[12] Early initiation of smoking and increase in the number of cigarettes consumed per day increases the cancer risk.[4] There is also a dose–response relationship with bidi smoking;[13] a multicentric case-control study showed bidi smoking to be a strong risk factor for developing hypopharyngeal cancer (odds ratio – 6.8) and supraglottic cancer (odds ratio – 7.5).[14] Smoking cessation is important as it decreases the risk of developing head and neck cancers.[15] Alcohol consumption with direct and indirect carcinogenic actions is also associated with hypopharyngeal cancers. Alcohol not only acts as a solvent for carcinogens like tobacco but also makes the mucosa more permeable to them. Wine, beer and liquor have similar risk of developing head neck cancers.[13, 16–18] There is a dose–response relationship between alcohol intake and

hypopharyngeal cancer[19] with a meta-analysis showing heavy drinkers (>4 drinks/day) having a relative risk of 9.03 compared to occasional or non-drinkers.[20] Those consuming dark liquors have been found to have 4.4 times relative risk compared to light liquors.[21]

HPV related cancers, though more common in the oropharynx, are seen in 10.9% of hypopharyngeal cancers with pyriform fossa having the highest association.[22, 23]

Diet and weight have a bearing in development of cancers. Lower body mass index (BMI) (<18.5) is associated with a greater risk of developing hypopharyngeal cancers.[24] and this seems to be particularly strong among current smokers.[25] Fruits, raw vegetables, and whole grain and dietary fibre intake have an inverse relationship with pharyngeal cancer while higher meat and fried food intake seem to increase the risk of developing hypopharyngeal cancers.[26–29] Post-cricoid tumours are commonly seen in women and are associated with sideropenic dysphagia (Paterson–Brown–Kelly syndrome/Plummer–Vinson syndrome). Certain occupations such as construction workers, potters, butchers, barbers and those exposed to formalin fumes, coal dust, steel dust, iron compounds and fumes are at a higher risk of developing hypopharyngeal carcinoma.[16, 30, 31]

MOLECULAR BASIS OF HYPOPHARYNGEAL CANCERS

Molecular changes causing hypopharyngeal cancers are similar to those at other head and neck sites. However, there are certain specific molecular factors that impact the prognosis of hypopharyngeal cancers. The hypopharynx cancer-specific literature identifies a correlation with amplification of oncogenes (*CCND1*, *FGF3* and *FGF4*) in the region of 11q12, and surprising lack of correlation with loss of tumour suppressor gene.[32] On the contrary, *p53* overexpression was seen in 66% of hypopharyngeal tumours and the overexpression or stabilization of *p53* was significantly associated with improved survival.[33] Cyclin D1 overexpression, apart from being predictive of multiple neoplasms, correlates with advanced clinical stage, tumour extension and relapse prediction after primary radiotherapy and survival.[34] Ki-67, a marker of cell proliferation, is indicative of poor survival.[35, 36] Amongst various factors such as p53, p21, Rb and Cyclin D1 studied in laryngeal and hypopharyngeal cancers, only Cyclin D1 has independent prognostic value for cancer-specific survival.[37] Amongst the growth factor receptors, EGFR was found to be overexpressed in 30% of hypopharyngeal cancers.[38] These may translate into biomarkers for early detection or treatment planning in the quest for personalized medicine.

HISTOLOGY

Most cancers of the hypopharynx are squamous cell in origin and tend to be moderately or poorly differentiated tumours, especially in the pyriform sinus. Non-squamous malignancies are rare and tend to arise from the minor salivary glands (mostly adenoid cystic carcinomas) or are mesenchymal in origin.

ROUTES OF SPREAD

Due to the lack of well-defined spaces as in the larynx, tumours of hypopharynx do not have a very well-defined pattern of spread within the laryngopharynx. With absence of barriers these cancers tend to grow and disseminate long before the patient is symptomatic.

Local extension

Tumours involving the lateral wall of the pyriform sinus most often invade the thyroid cartilage, with ossified cartilages being more prone to tumour invasion. Tumours involving the medial wall of the pyriform sinus extend antero-medially into the paraglottic space and impede vocal cord movement either by mass effect or by invasion of the intrinsic muscles. The apex of the pyriform sinus being inferior to the paraglottic space, tumours tend to involve the paraglottic space early causing cord fixity. Tumours at the pyriform apex can also escape through the cricothyroid membrane and involve the thyroid gland (**Figure 16.2**).[39] Tumours at the pyriform apex do not lend themselves to any form of partial laryngo-pharyngectomy that preserves speech as well as nasal respiration, since the oncological resection would entail removal of the cricoid cartilage. The proximity to the intrinsic laryngeal muscles, the cricoarytenoid joint and the recurrent nerve leads to early impairment of the vocal cords by the tumours.[40, 41]

Post-cricoid area tumours tend to invade the cricoid and tracheal cartilages,[42] thus involving the airway and causing obstruction. The tumour may infiltrate the posterior cricoarytenoid muscle and cricoarytenoid joint causing cord fixity and even precipitate aspiration. Post-cricoid tumours also tend to extend exolaryngeal through the cricothyroid membrane to involve the thyroid gland (**Figure 16.4e**).

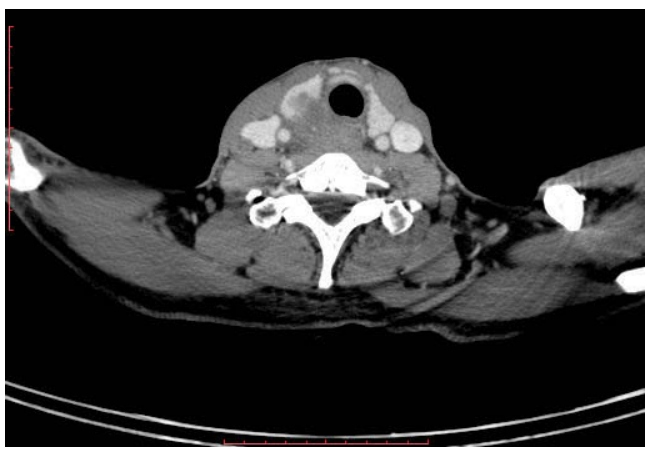

Figure 16.2 Right hypopharyngeal cancer with thyroid gland invasion presenting as a thyroid mass.

Anterolateral spread from a predominantly submucous infiltrative post-cricoid cancer may present with a swelling in the region of the thyroid and may be misdiagnosed as goitre, especially in cases where the dysphagia is minimal. It must be pointed out that both these conditions, i.e. post-cricoid cancer and goitre, are commonly seen amongst young females. There have been instances when such mistaken diagnosis has led to exploration of the neck for thyroidectomy causing a lot of embarrassment to the surgical team (**Figure 16.2**).

Post-cricoid lesions have significant submucosal spread which is more pronounced inferiorly than superiorly.[43] The extension of the disease into the cervical oesophagus is common with occasional skip lesions in the oesophagus due to the submucosal lymphatic plexus. This mandates careful pre-treatment evaluation and planning as it can alter the treatment plan.

Lateral spread (parapharyngeal) is in the vicinity of the carotid sheath and extralaryngeal spread from the hypopharyngeal and supraglottic cancers often encases the carotid vessels which needs careful evaluation to differentiate from nodal disease (**Figure 16.3**).

Posterior pharyngeal wall tumours are relatively less common and have not been studied extensively. The tumours tend to be exophytic and are frequently large at the time of diagnosis. In spite of this, invasion of the prevertebral fascia occurs late. The tumour usually involves adjacent areas when first diagnosed. The tumour may extend superiorly to the base of the tonsil and laterally to the oropharyngeal wall, or spread inferiorly into the post-cricoid region and cervical oesophagus. Synchronous tumours along the pharyngeal wall should be evaluated due to the continuous mucosa and extensive lymphatics.

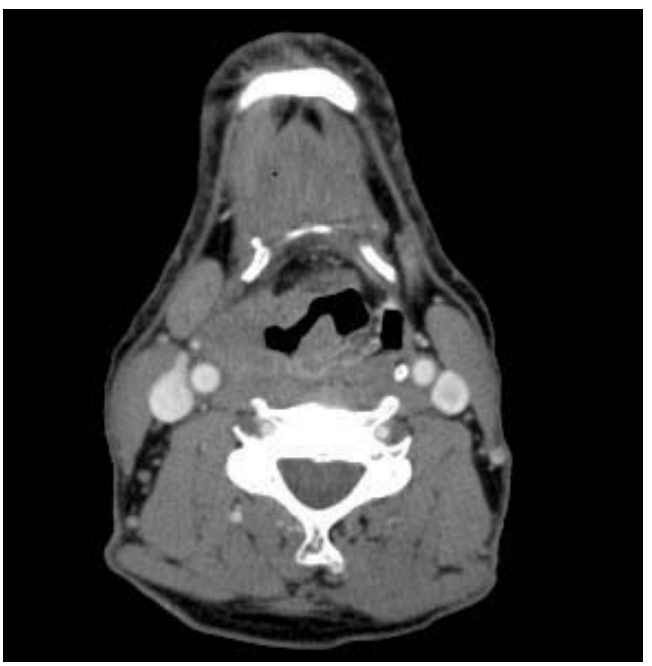

Figure 16.3 Right hypopharyngeal cancer demonstrating extralaryngeal extension.

Regional spread

Hypopharyngeal tumours have the highest propensity for early lymph nodal metastases. Up to 70% of patients may have lymph nodal metastases particularly to levels II and III at presentation and there is a high incidence of occult nodal metastases, which will influence the investigations, staging and treatment.[44] Paratracheal and paraoesophageal i.e. level VI metastases are more common in lesions involving post-cricoid or pyriform sinus apex while retropharyngeal nodes can be involved in posterior pharyngeal wall cancers.[45, 46] When patients have unilateral clinically positive neck disease, the incidence of contralateral occult lymph node metastases is at least 50%.[47] Bilateral occult lymph node metastases in patients with clinically negative neck are most frequently associated with cancers of the pyriform sinus (**Figure 16.1**).[47, 48] In patients with clinically positive neck disease, more than 20% have involvement of the lower nodal stations (level IV and V).[48]

Distant spread

Among all head and neck cancers, hypopharyngeal primaries have the highest incidence of distant metastases at presentation (17–24%)[49, 50] and during follow-up, with more than 50% of failures due to distant metastases.[51] Pulmonary metastases are most common followed by skeletal and liver metastases. The average survival is usually less than 1 year once distant metastases have been diagnosed.[52] Development of distant metastases at some time following initial treatment is associated with tumour recurrence locoregionally.[53]

CLINICAL PRESENTATION

Symptomatology

Hypopharyngeal tumours are detected late as the patients are asymptomatic in the early stages, especially those involving the pyriform sinus. The cardinal symptoms are odynophagia, dysphagia, hoarseness, otalgia, weight loss or a neck lump. The earliest symptom may be that of mild non-specific throat discomfort. In fact, globus sensation may be the only presenting complaint with normal clinical findings.[54] Dysphagia to solid food may be an early presentation in post-cricoid cancers, but is generally seen late in pyriform cancers. Significant weight loss is especially seen in post-cricoid area and oesophageal tumours. Unilateral referred otalgia, is another common symptom and may indicate involvement of Arnold's nerve (X) as explained before. Occasionally, in advanced cases, where the disease extends superiorly to involve the tongue base, referred otalgia may be present deep in the ear, mediated via the glossopharyngeal nerve, the pharyngeal plexus and the Jacobson's nerve in the middle ear. Hoarseness of voice may be a late presentation in pyriform and post-cricoid cancers while 'hot potato' speech signifies involvement of the base of the tongue. As discussed before, a significant

proportion of patients may present to the clinic with palpable neck lymphadenopathy as the only complaint on initial clinical examination.

Clinical examination and signs

A careful and detailed history taking and examination of the patients with suspected hypopharyngeal cancers must be done in the clinic. Most of these patients tend to be elderly males except those with post-cricoid tumours, which is seen predominantly amongst females. A history of tobacco and alcohol consumption must be elicited and recorded with respect to quantity and duration. Counselling services must be offered for tobacco and alcohol cessation, if the patient is continuing with the habit. Patients with advanced disease may look unwell, with significant weight loss. Halitosis may be present. The patients may appear to attempt swallowing with discomfort frequently and a noticeable lump may be present in the neck on inspection. Hoarseness of the voice and history of aspiration must be recorded in every case. In advanced disease, there can be airway compromise with stridor on presentation.

On examination, the presence of exolaryngeal spread with widening of the thyroid cartilage must be assessed. Loss of laryngeal crepitus (Trotter's sign) and restriction of neck extension may imply involvement of the prevertebral fascia. The neck must be carefully palpated for nodes and their size, level of involvement and laterality recorded meticulously. In case of large nodes, movement of the node in vertical and horizontal axis, fixity to the carotid sheath and consistency of nodes (solid or necrotic) must be noted. Skin and platysma involvement must be documented. The root of neck at the suprasternal space of Burns needs to be evaluated for tracheal displacement as well as palpable disease or lymph nodes which would suggest unresectability.

On laryngeal examination, either with a Hopkins rod telescope or mirror, the presence of a growth should be observed. Pooling of saliva may obscure the growth especially in pyriform cancers. If a growth is noted, the extent of disease and involvement of hemi-larynx should be noted. A fibre-optic endoscopic examination under local anaesthesia would give additional visualization and help document the disease extent especially in posterior pharyngeal and pyriform growths. Additionally, a biopsy may be taken with use of the flexible forceps passing through the biopsy channel. However, the flexible endoscope may not be adequate to visualize the inferior extent of the disease, particularly the apex of pyriform sinus and post-cricoid area. In these cases, rigid pharyngoscopy should be performed under general anaesthesia. Treatment decisions are guided by the tumour map, which highlights the importance of a good clinical and laryngoscopic evaluation. In case of circumferential lesions of post-cricoid going down into the cervical oesophagus, a flexible oesophagoscopy may be better than a rigid oesophagoscopy to document the inferior extent of disease as well as to look for a second primary in the oesophagus. A checklist used at the time of the evaluation is important to avoid missing details and has implications for treatment planning (**Table 16.1**).

DIAGNOSIS AND STAGING

Investigations

Barium oesophagogram is an effective screening tool for hypopharyngeal cancers and synchronous cancers in the oesophagus. Barium swallow helps determine the lower limit of a post-cricoid cancer, information that is very vital in the treatment planning.[55] Current practice in most centres involves a flexible transnasal oesophagoscopy to map the lesion, determine its lower limit and proximity to the cricopharynx, assess oesophageal involvement and evaluate synchronous primaries in the oesophagus. This supersedes barium imaging.

Direct laryngoscopy under general anaesthesia helps obtain a biopsy and assess the extent of the lesion for treatment planning. In case of a palpable neck node, biopsy confirmation may be obtained with fine-needle aspiration cytology (FNAC). Open biopsy must be avoided.

Compared to endoscopy or manual examination, CT imaging has higher sensitivity for defining the T stage of the primary tumour (size of tumour, relationship to critical deep structures). Adequate imaging includes contrast enhanced CT (CE-CT) performed with a multidetector CT scanner with bone window reformats (for cartilage assessment).[56] For assessment of cartilage invasion, MR imaging seems to be more sensitive than CT (sensitivity up to 96%). However, CE-CT is the first choice for imaging with MR reserved for trouble shooting. Both CT and MRI over diagnose posterior tumour spread in advanced hypopharyngeal disease and should be correlated clinically. The imaging reporting should be synoptic to avoid missing critical information. The synoptic essentials are covered in **Table 16.2**. **Figure 16.4** illustrates the range of radiologic findings in hypopharyngeal primaries.

A chest X-ray should be performed as a part of screening for distant metastasis while a CT chest is indicated in all patients with advanced stage tumours and/or bulky neck disease.[57] In borderline-resectable disease, positron emission tomography (PET) along with CT scan (FDG-PET/CE-CT) as a single-staging investigation may be considered for evaluation of the primary disease status and excluding any occult distant disease.[58–61] FDG PET/CE-CT is a useful imaging modality in the assessment of laryngeal and hypopharyngeal cancers, especially in post-radiation residual/ recurrent disease where it is often very difficult to prove the presence of active disease and differentiate it from post-radiation oedema.[62]

Staging

Staging of hypopharyngeal cancer is carried out according to the TNM classification, (**Table 16.3**). For the larynx and hypopharynx the only change from the previous staging has been the renaming of T4a resectable as T4a (moderately advanced) and T4b unresectable as T4b (very advanced).

TABLE 16.1 Checklist for direct laryngoscopy under anaesthesia

Subsite evaluated during endoscopy	Disease status	Implication
Oropharynx		
Vallecula /base tongue	Involved / free If involved lateralized or crossing midline	If lateralized resectable If crossing midline, decision-making for glossectomy with laryngectomy vs. chemoradiation
Inferior tonsil pole	Close / involved / free	Close – resectable but will need pharyngeal reconstruction Involved – to evaluate for resectability with superior and lateral extent of lesion into parapharyngeal space
Hypopharynx		
Pyriform apex	Involved / free	No conservation laryngeal procedure feasible as cricoid cannot be oncologically preserved
Cricoartyenoid joint	Involved / free	
Arytenoid cartilage	Involved / free	If cricoarytenoid joint is mobile, consider replacing posterior glottic bulk if conservation laryngeal procedure is planned
Cricopharynx	Free / involved / extending to oesophagus	Involvement indicates circumferential pharyngeal resection requiring reconstruction with free jejunum or free radial artery flap Oesophageal involvement indicates need for gastric pull-up
Lateral pyriform wall	Involved / free	Pharyngotomy approach and pharyngeal reconstruction
Posterior pharyngeal wall	Involved / free If involved lateralized or crossing midline	Crossing midline – pharyngeal reconstruction needed
Pharyngeal mucosa	Mobile / fixed	Mobile – consider TLM / RT Fixed – non-surgical modality
Post-cricoid	Involved / free	Near-total laryngectomy is not feasible and may require patch pharyngoplasty
Glottis / supraglottis		
Vocal cords	Mobile / impaired / fixed	Mobile cords – TLM/TORS,/OPL/ RT Fixed cords – organ preservation
Pre-epiglottic space	Involved / free	Free TLM/TORS/ OPL / RT Involved – organ preservation
Paraglottic space	Involved / free	
Anterior commissure	Cords mobile and pre-epiglottic space free	Supracricoid laryngectomy/hemipharyngectomy
Subglottis	> 1 cm anteriorly	No conservation laryngeal surgery possible
	< 5 mm posteriorly	
Inter-arytenoid	Involved	Conservation laryngeal surgery and near-total laryngectomy not feasible.

TABLE 16.2 Synoptic radiological report

- Tumour volume
- Locoregional extent of the disease
  - Superior – Oropharynx
  - Inferior – Cricopharynx, oesophagus
  - Transglottic
  - Crossing midline – anterior commissure, post cricoid
- Pre-epiglottic space and paraglottic space
- Exolaryngeal spread – thyrohyoid membrane, cricothyroid membrane, straps muscles
- Thyroid and cricoid cartilage involvement
- Cricoarytenoid joint
- Visceral spaces (prevertebral fascia, carotid space)
- Metastatic lymph nodes - Levels II-V, Paratracheal, Retropharyngeal

FACTORS DETERMINING TREATMENT IN HYPOPHARYNGEAL CANCER

Treatment decisions in cancer are guided by the biology of the disease and the peculiarities of the organ affected. Tumour and nodal factors, performance status (PS) of the patient, resources and available technical expertise dictate the management.

Tumour factors: Squamous cell cancers are biologically more aggressive in the hypopharynx due to its rich vascularity and lack of barriers to the spread of tumour. Hypopharyngeal tumours uniquely have substantial submucosal spread well beyond the mucosal limits of the tumour and are seen up to 20 mm.[63] Whole organ studies of hypopharyngeal cancer specimens showed submucosal spread in 60%, most being in the inferior direction followed by lateral and superior. The submucosal spread is not obvious macroscopically and is more often seen in post-irradiated patients.[64] Surgical margins should be critically assessed to contain this submucosal spread.

Proximity of hypopharynx tumours to the larynx causes them to affect laryngeal functions.[65] Surgical organ preservation procedures should be planned based on structural and functional integrity of the larynx without compromising oncologic safety.

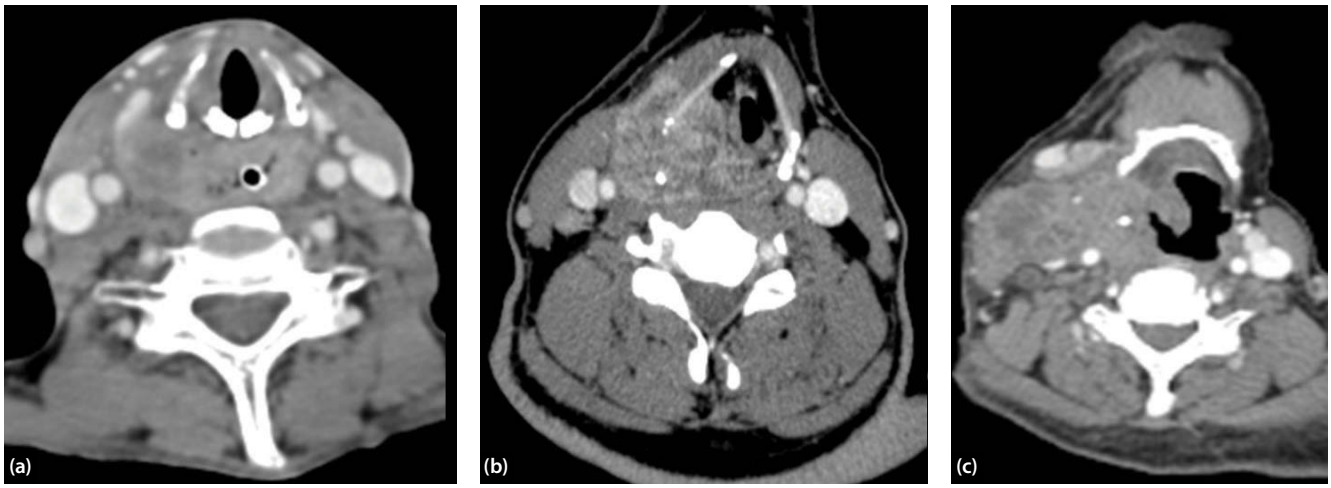

Figure 16.4 **(a)** Extension into post-cricoid region with extralaryngeal component: T3. **(b)** Involving the outer cortex of thyroid cartilage with extralaryngeal spread that surrounds less than 180° of the carotid artery. **(c)** Extralaryngeal spread with involvement of prevertebral fascia and splaying of carotid vessels: T4b.

Nodal factors: Hypopharynx is rich in lymphatics with a high incidence of metastasis to the jugular paratracheal and retropharyngeal group of lymph nodes even in early stages of the disease which may result in the nodal disease as the primary manifestation in 65% to 80% and occult metastasis in 30% to 40% of N0 necks.[43, 48, 66–68] Hence treatment of neck nodes is mandatory in all hypopharyngeal cancers.[69]

Performance status: PS is a measure of general condition of the patient. It takes into account their general wellbeing and ability to carry on daily life activities. Usually the PS scales are the Karnofsky score or the WHO / ECOG / Zubrod scale.

PS in hypopharyngeal cancers is important estimate of treatment outcomes:

- Conservative surgery both open and transoral methods will alter laryngeal anatomy and physiology, resulting in alteration of laryngeal protection mechanisms, thus increasing the probability of aspiration and dysphagia. PS is an important estimate of the ability of the patient to withstand sequelae of the surgery.
- More than 75% of patients present in advanced stages III and IV and will go on to receive multimodality treatment. If PS is low, the possibility of withstanding and completing treatment is lower.
- In the palliative care setting, PS helps determine if the patient will benefit from either chemotherapy or radiation or is best suited for only supportive care.

Resources and technical expertise: Transoral surgery in select cases is technically demanding as well as resource heavy. Transoral laser and robotic surgery require intensive training and mentorship. The goal is to reduce morbidity of multimodal therapy without compromising oncological outcomes; hence achieving proper clearance of disease through transoral access is paramount. Resources such as a fully equipped microlaryngeal setup with laser or a transoral robotic setup are required and may not be feasible at all centres.

Partial laryngopharyngeal resection requires proper case selection and training in laryngeal conservative surgery and reconstructive techniques.

Radiation therapy and chemotherapy are challenging in patients who are nutritionally depleted, who will experience higher grade toxicity with concomitant chemotherapy regimes, resulting in noncompliance with treatment schedule and poorer outcomes. Expertise in delivery of these technically demanding therapies is required for optimal outcomes.

TREATMENT OF EARLY HYPOPHARYNGEAL CANCERS

Early cancers are potentially curable and the goals of treatment should be maximizing chances of cure with function preservation. In hypopharyngeal cancers, these goals are impeded by the proximity of the larynx and occult metastatic nodes, even in early staged tumours.

Treatment of T1 and T2 hypopharyngeal cancers can be with either radiation therapy or conservation surgery. Decision-making in early hypopharyngeal cancers depends on the tumour location and the ability of the patient to withstand treatment. Oncological safety and functional preservation are important decision-making criteria while choosing treatment.

Larynx conservation surgery

Surgical considerations are similar to those in laryngeal cancers where preservation of speech and larynx protection mechanisms is paramount. Patient age and respiratory function are very important selection criteria because hypopharyngeal resection combined with partial laryngectomy alters voice and increases risk of aspiration and airway compromise. Hence patients with tumours involving

TABLE 16.3 UICC staging 8th edition

Primary tumour	
T1	Tumour limited to one subsite of hypopharynx and/or 2 cm or less in greatest dimension
T2	Tumour invades more than one subsite of hypopharynx or an adjacent site, or measures more than 2 cm but not more than 4 cm in greatest dimension without fixation of hemilarynx
T3	Tumour more than 4 cm in greatest dimension or with fixation of hemilarynx or extension to oesophagus
T4a	Moderately advanced local disease. Tumour invades thyroid/cricoid cartilage, hyoid bone, thyroid gland, or central compartment soft tissue (includes prelaryngeal strap muscles)
T4b	Very advanced local disease. Tumour invades prevertebral fascia, encases carotid artery, or involves mediastinal structures
Regional lymph nodes (N)	
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension without extranodal extension
N2a	Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension without extranodal extension
N2b	Multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension without extranodal extension
N2c	Bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension without extranodal extension
N3a	Metastasis in a lymph node, more than 6 cm in greatest dimension without extranodal extension
N3b	Metastasis in a single or multiple lymph nodes with clinical extranodal extension*

Stage grouping

Group	T	N	M
0	Tis	N0	M0
I	T1	N0	M0
II	T2	N0	M0
III	T3	N0	M0
	T1, T2, T3	N1	M0
IVA	T1, T2, T3	N2	M0
	T4a	N0, N1, N2	M0
IVB	T4b	Any N	M0
	Any T	N3	M0
IVC	Any T	Any N	M1

* Presence of skin involvement or soft tissue invasion with deep fixation / tethering to underlying muscle or adjacent structures or clinical signs of nerve involvement is classified as clinical extranodal extension. Midline nodes are considered ipsilateral nodes.

the pyriform apex or post-cricoid area and those with poor pulmonary function should not be considered as candidates for partial pharyngolaryngectomy. Gastrostomy tube and tracheostomy tube dependence is also a real possibility with alteration of laryngopharyngeal anatomy with surgery and post-operative radiation therapy.

The larynx conservation surgery for early hypopharyngeal cancers can be via two approaches: conventional external and transoral approaches.

EXTERNAL APPROACH – PARTIAL LARYNGOPHARYNGECTOMY

Indications

Conservation surgical procedures are considered for early lesions of the hypopharynx:

- Tumours less than 4 cm (T1–T2)
- Pyriform apex and post-cricoid mucosa free of disease
- Mobile vocal cords
- No erosion of the thyroid cartilage
- No paraglottic spread.

Types

The choice of conservation surgical techniques depends on the location and the spread of the tumour. Depending on the proximity of the lesion to the larynx the procedure can be either partial pharyngectomy, or partial pharyngolaryngectomy.

Partial pharyngectomy: When the tumour arises on the pharyngeal component of the hypopharynx and spares the medial wall of the pyriform sinus and the apex, it is suitable for partial pharyngeal resection. Approached through a lateral pharyngotomy, the involved pharyngeal wall is resected and reconstructed with either pectoralis major myocutaneous flap or free flap. The pharyngeal reconstruction restores continuity of the upper aerodigestive tract and with it, normal speech and swallow.

Partial pharyngolaryngectomy: When the tumour involves the medial wall of the pyriform sinus and extends onto the supraglottic structures of the larynx it necessitates partial resection of the hypopharynx and the larynx. Partial pharyngectomy can be either an extended supraglottic partial laryngectomy or supracricoid hemilaryngopharyngectomy. It is a functional procedure involving resection of the hemilarynx above the level of the cricoid and the medial aspect of pyriform sinus and the ipsilateral supraglottic structures (**Figure 16.5a**). The laryngeal functions are impeded with loss of sensation due to resection of superior laryngeal nerve and removal of supraglottic structures. These need to be reconstructed to prevent aspiration, stridor and dysphagia.

RECONSTRUCTION FOLLOWING PARTIAL LARYNGOPHARYNGECTOMY

Following partial laryngopharyngectomy, the goals of reconstruction are to restore not only the anatomical continuity but also the functionality of the larynx viz airway protection, airway preservation and the ability to voice. The pharyngeal defect is reconstructed with either the pectoralis myocutaneous flap or the free flap usually the radial forearm flap (**Figure 16.5b**). The laryngeal

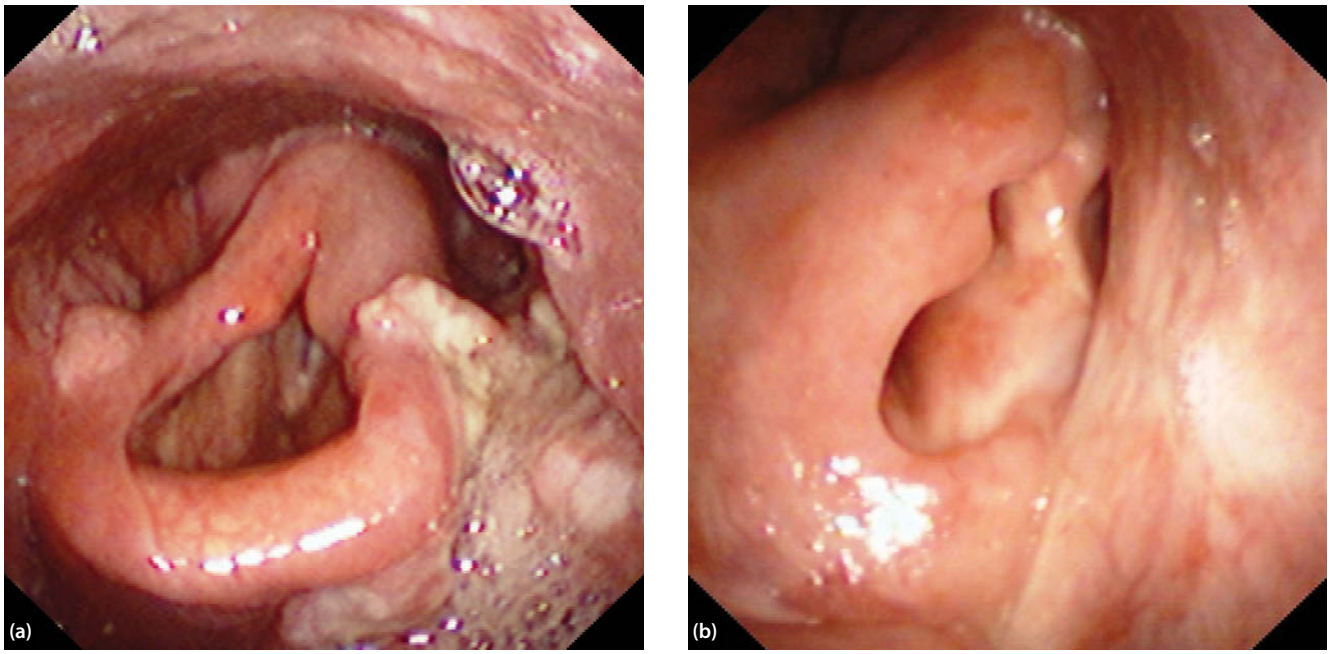

Figure 16.5 **(a)** Early hypopharngeal tumour treated by open partial laryngopharyngeal resection and free radial forearm flap reconstruction, **(b)** shows a healthy pyriform at two years with minimal disruption of anatomy. Note lack of pooling indicating good swallowing function (Courtesy of Prof. Rudolf Hagen, Germany).

structures will be reconstructed ingeniously using parts of the epiglottis and hyoid. Microvascular free-flap expertise has tremendously improved outcomes as compared to the 1960s and 1970s with lower rates of morbidity.

Oncological outcomes

Several studies analyzed the results obtained with partial surgery in patients with early pyriform sinus carcinoma.[49, 70, 71] with 5-year overall survival rates ranging from 55% to 59%. The local control rates have often been excellent ranging from 77% to 97% while regional recurrences occur in 15–23% and distant metastases in 28%. In most series, the incidence of distant metastasis increases as the local control rates improve. Survival is better in patients with T1 disease, those with good surgical margins and in those receiving post-operative radiation.[72–74] Extension to the apex of the pyriform sinus is fraught with local failure while distant metastases occur in patients with two or three wall involvements.[49] Amongst the contemporary series, Chung et al[75] reported 58 patients who underwent partial pharyngectomy with reconstruction, showing 5-year overall and disease specific survival rates of 78% and 77.6% respectively. Level VI metastasis confirmed by histopathological analysis, close (< 5 mm) histologic margins, advanced nodal stage and posterior pharyngeal wall tumours were significant independent factors associated with poor disease-specific survival.

Functional outcomes

Conservation surgery entails removal of structures involved in laryngeal protection. The long-term functional issues are aspiration, tracheostomy and gastrostomy. The published literature suggests that the majority of patients achieve deglutition without aspiration. However, there is a real possibility of aspiration leading to pulmonary infection and death. Even from experienced centres a 3.7% post-operative mortality is reported.[76] Aspiration-free swallowing is generally restored in two-thirds of cases by the end of the first month and in the rest up to 1 year after surgery. However, 3–5% of cases either die of aspiration or undergo completion total laryngectomy or a permanent gastrostomy. With microvascular free-flap reconstruction, the contemporary series show better results. Chung et al[75] in their series of 58 patients reconstructed the pharynx in 72%, majority with free-radial forearm flap. Post-operative pharyngocutaneous fistula developed in 10.3% of which two required PMMC reconstruction for closure. Oral feeding was achieved in 86.2% patients within a mean of 26 days while 13.8% required percutaneous endoscopic gastrostomy tube. Eighty-eight per cent could be decannulated within a mean of 44 days post-operatively. Hence proper patient selection and use of appropriate reconstruction of the laryngopharyngeal defect is important to succeed with the intended functional laryngeal preservation.

TRANSORAL APPROACHES

The transoral approach for surgical resection of the hypopharyngeal cancers can be undertaken either with transoral laser microsurgery or transoral robotic surgery. A new technique, transoral videoendoscopic surgery, has recently been described.

Indications are similar to the open approaches

- tumours less than 4 cm (T1–T2)
- pyriform apex and post-cricoid mucosa free of disease

- good exposure
- mobile vocal cords.

Contraindications:

- oral submucous fibrosis
- full thickness involvement of the pharyngeal muscles
- thyroid cartilage involvement
- base tongue and arytenoid involvement
- cervical oesophagus involvement.

Advantages over open approach:

- avoid disruption of laryngeal skeleton and soft tissues
- avoid tracheostomy
- preservation of innervation
- prevention oro-cervical fistula formation.

Transoral laser microsurgery (TLM)

This transoral approach uses CO_2 laser coupled to the microscope to resect hypopharyngeal tumours. The advantages of laser are precise resection with minimal collateral thermal damage. With minimum alteration of anatomy, there is negligible aspiration and early restoration of oral feeding. Case selection for organ conservation in hypopharyngeal cancers is based on the amount of margin possible with preservation of structures to retain a functional larynx. Besides the larynx, the pharyngeal resection should not expose neck structures requiring additional surgery.

Oncological outcome

The efficacy of TLM in hypopharyngeal cancers should be analyzed in terms of organ preservation and local control. In Steiner's series,[77] transoral CO2 laser surgery was performed on 172 patients, of whom 33 were stage I and II pyriform sinus carcinoma. The 5-year local control was 84% for T1, 70% for T2, 75% for T3 and 57% for T4a tumours. The 5-year recurrence-free survival was 73% in stage I and stage II disease, 59% in stage III disease and 47% in stage IVa disease. Rudert et al[78] in their series of 29 hypopharyngeal cancer patients treated with TLM reported a 5-year overall survival of 71% in stage I and stage II tumours and 47% in stage III and stage IV tumours. In these series, the highest local control rate was achieved in tumours involving the lateral hypopharyngeal wall. In the final analysis, the outcome is significantly dependent on the lymph node involvement as in most head and neck squamous cell cancers. While deciding on the treatment options, functional preservation and oncological safety are important considerations, especially when a lesser morbid treatment option is available. TLM of hypopharynx shows comparable results with open surgical procedures and is superior to radiotherapy alone in terms of organ preservation and local recurrence rate.

Functional outcomes

Post-operative recovery following endoscopic resection of even large hypopharyngeal cancers is surprisingly smooth. If the arytenoid is preserved, most patients are on oral feeds from the first post-operative day. Aspiration depends on preservation of structures and innervation. The healing process is rapid and usually is not a major problem. Hence the procedure is feasible even in the elderly and those with chronic obstructive pulmonary disease (COPD). Mild to moderate discomfort on swallowing may persist for about a week.

Following resection of a large tumour, the resultant raw area necessitates tube feeding for a few days. If the arytenoid is resected, aspiration may be a problem in the post-operative period. In most series[79, 80] functional preservation was seen in 80% of patients. More than one-third of patients do not need nasogastric feeding following TLM, while in the rest the tube feeding remains for around 10–14 days. Post-operative aspiration pneumonia is seen in less than 12% of patients and the need for tracheostomy arises in 5% of patients.

Steiner and Ambrosch report two patients out of 129 cases of pyriform sinus cancer where oral feeding could not be resumed because of persistent aspiration.[77] Pradhan et al[81] have reported persistent aspiration necessitating a feeding gastrostomy in two patients where the arytenoid was resected out of 109 cases of early hypopharyngeal and supraglottic tumours. Both these were cases of recurrent disease in the pyriform sinus 5 years and 13 years following treatment with radiation therapy.

Transoral robotic surgery (TORS)

Another transoral approach which has evolved in the past decade is TORS. It is technologically improved on the standard microscopic and endoscopic techniques in terms of 3D-vision, magnification and ability to operate outside the line of sight. The TORS facilitates two- to four-handed surgery without tremors and improved dexterity. A transoral resection is performed with electrocautery tip similar to open surgery with the added advantage of transoral route with minimal anatomical changes.

TORS is currently done with the da Vinci robotic system® with three arms, one for the camera which has full HD capability with two endoscopes and a 10 x magnification (**Figure 16.6**). TLM is limited with the need for line of sight for firing the laser beam. This is overcome with angled vision and the degrees of freedom for the wristed robotic arms. There is also the advantage of active control of larger blood vessel bleed with use of electrocautery and two-handed approach. The use of TORS for hypopharyngeal cancers has begun recently and long-term results are awaited.

Park et al[82] from Yonsei University, Seoul, Korea published their results of 23 patients managed by TORS with an overall survival of 89% and disease-free survival of 84% at 3 years. On objective evaluation, serious aspiration or delay of swallowing was not observed during the pharyngeal stage of the swallowing process. Overall, 96% of the patients showed favourable swallowing abilities.

There are also reports of combining fibre CO_2 laser with the robotic arm to get that additional advantage of reduced collateral thermal damage as compared to the electrocautery. However, it remains to be seen if the TORS

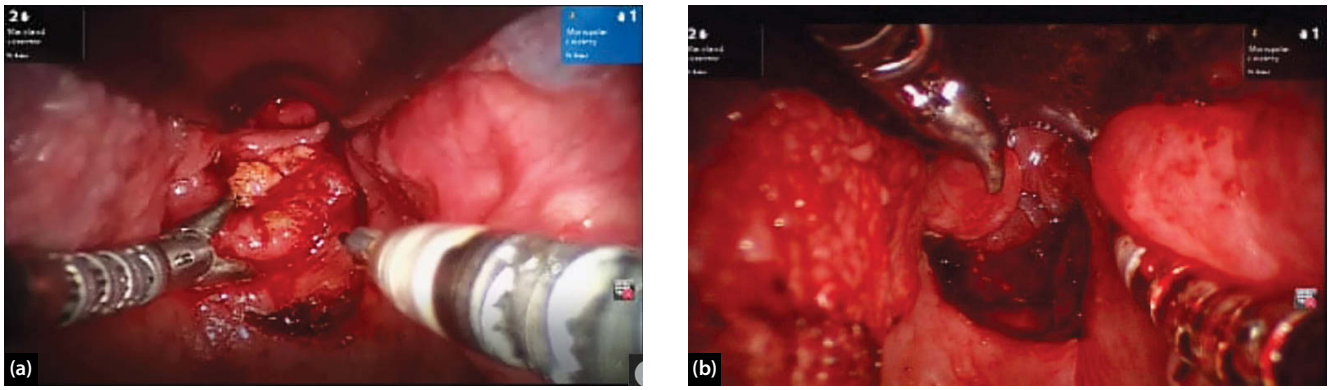

Figure 16.6 Transoral robotic resection of a posterior pharyngeal wall tumour **(a)** the defect is left to heal by secondary intention **(b)** (Image courtesy of Prof. Vinidh Paleri, London).

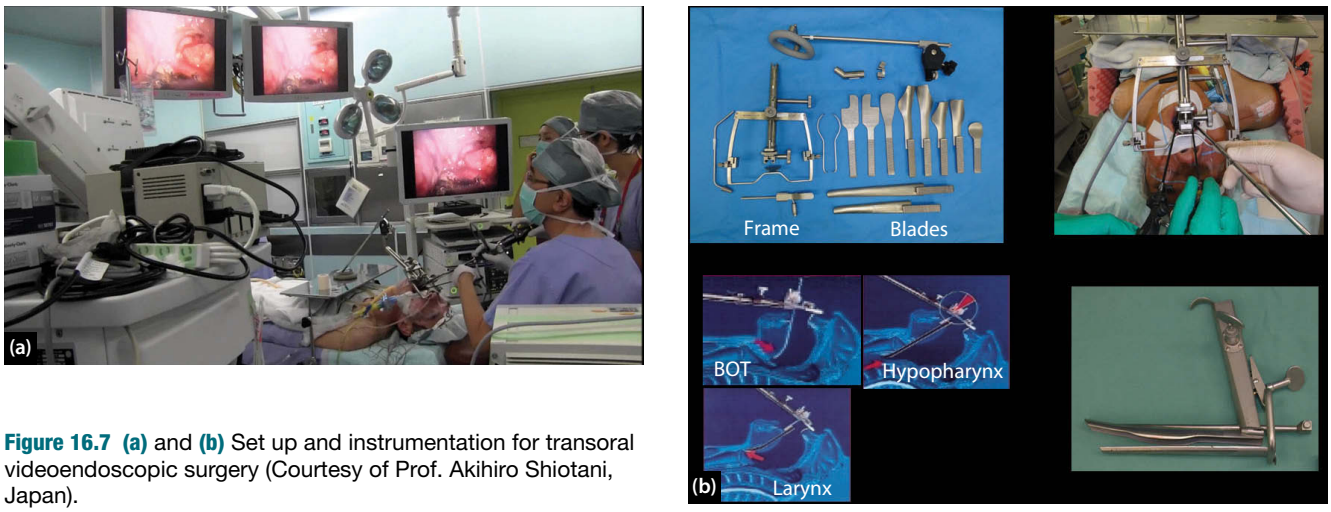

Figure 16.7 **(a)** and **(b)** Set up and instrumentation for transoral videoendoscopic surgery (Courtesy of Prof. Akihiro Shiotani, Japan).

scores over TLM in oncological and functional outcomes besides ease of surgery and the morbidity of the procedure.

Transoral videoendoscopic surgery (TOVS)

TOVS uses flexible video endoscope to visualize the lesion through a suspended larynx similar to microlaryngoscopy (**Figure 16.7**). The difference is the utilization of the video endoscope to visualize the lesion and use of curved instruments with electrocautery for resection. The inspiration for TOVS comes from the endoscopic mucosal resections carried out in the oesophagus by the gastrointestinal surgeons, which, akin to early cancers of the hypopharynx, are predominantly mucosal diseases. The procedure is relatively new and early results are promising. The Japanese series show promising early results with technical feasibility, use of available equipment and outcomes. The long-term oncological outcomes are awaited with early reports from Shiotani et al showing 95% 3-year disease-free survival[83, 84] and good voice and swallowing outcomes.[85, 86]

MANAGEMENT OF THE NECK

All patients should be assessed with CT scan and ultrasonography (USG) as complementary tools to discern metastatic nodes. Patients with pT_1N_0 tumours are either followed up with a wait and watch policy for the neck, with regular US every 2–3 months in the first 2 years, then every 6 months or undergo ipsilateral selective neck dissection of levels II, III and IV. In patients with suspected occult metastatic neck nodes on imaging, unilateral or bilateral neck dissection is performed, depending on the imaging and site of primary. The neck dissection is usually a selective neck dissection of levels II, III and IV and evaluated on frozen section; if disease is found to be positive a modified radical neck dissection is performed. Where facilities for frozen section do not exist, further adjuvant treatment is based on histological report of the neck dissection specimen. In patients with larger tumours (T3–T4) Martin et al[87] recommend a bilateral neck dissection.

In open partial surgery, with the neck exposed for access, the ipsilateral levels II and III that are at the highest risk of occult metastasis are dissected. If they are obviously metastatic or on frozen section they appear involved, then a comprehensive neck dissection of levels II to V is carried out. In case of clinically palpable cervical lymph node metastasis, bilateral comprehensive neck dissection is performed.

ADJUVANT THERAPY FOLLOWING TRANSORAL APPROACHES IN EARLY CANCER

Following resection of T1/T2 hypopharyngeal cancer adjuvant radiation therapy is advised for tumour factors

such as positive margins, where re-resection is not suitable and for metastatic neck node disease. Fields of radiation include the primary tumour as well as both sides of the neck.

It must be highlighted here that TLM of hypopharyngeal cancer should not be performed to merely debulk the tumour. The intent must always be to achieve a complete resection with tumour-free margins.

Radiation therapy in early hypopharyngeal cancers

The goal of radiation therapy as a single modality in early hypopharyngeal tumours is to achieve an oncological cure with minimal toxicity, preserving both organ and function. Conventional external beam radiotherapy (EBRT) is usually delivered over a period of 6–7 weeks, with daily fractionation, 1.8–2 Gray (Gy) per fraction, 5 days a week, over a period of 6–7 weeks. Conformal radiotherapy with 3D planning or intensity-modulated radiation therapy (IMRT) is preferred to minimize radiation to normal structures and reduce xerostomia (**Figure 16.8**).

An analysis of 101 patients with T1–T2 carcinoma of the pyriform sinus treated at the University of Florida[88] with radiotherapy (RT) with or without a planned neck dissection for organ preservation demonstrated 5-year local control rates of 90% for T1 cancers and 80% for T2 lesions. The absolute survival rates for stage I and II were 57% and 61% respectively. Moderate to severe long-term complications developed in 12% of patients. RT alone or combined with a planned neck dissection can result in local control with larynx preservation in a high proportion of patients. The chance of cure is comparable to that observed after conservation surgery, and the risk of major complications is low.

A multi-institutional Japanese study[89] of 115 patients (39 Stage I and 76 Stage II) was carried out where 98 patients were treated with conventional fractionation RT and twice-daily RT in 17 patients. Chemotherapy was combined with RT in 57 patients. With a median follow-up of 47 months the 5-year overall and disease-specific survival rate for 95 patients without synchronous malignancies was 66.0% and 77.4% respectively. The 5-year disease-specific survival rate was 95.8% for T1 and 70.1% for T2 disease. Local control with laryngeal voice preservation was achieved in 87% of T1 lesions and in 73.6% of T2 lesions. Synchronous or metachronous cancers developed in 56.5%. Early hypopharyngeal cancers tend to have a good prognosis with RT. However, second malignancies have an adverse effect on the overall outcomes of patients with early hypopharyngeal cancer.

TREATMENT OF ADVANCED HYPOPHARYNGEAL CANCERS

Advanced hypopharyngeal cancers pose a challenge for the treating oncologists. Many of them present with severe dysphagia, weight loss and malnutrition that needs active intervention by insertion of feeding tubes and dietary supplementation, prior to starting any therapy. It is important to make a proper assessment of the patient's PS and ability to tolerate and withstand major surgery and/or chemoradiation. The choice of initial therapy is based not just on age, PS, medical comorbidity but also on tumour characteristics such as extent of disease, presence of aspiration,

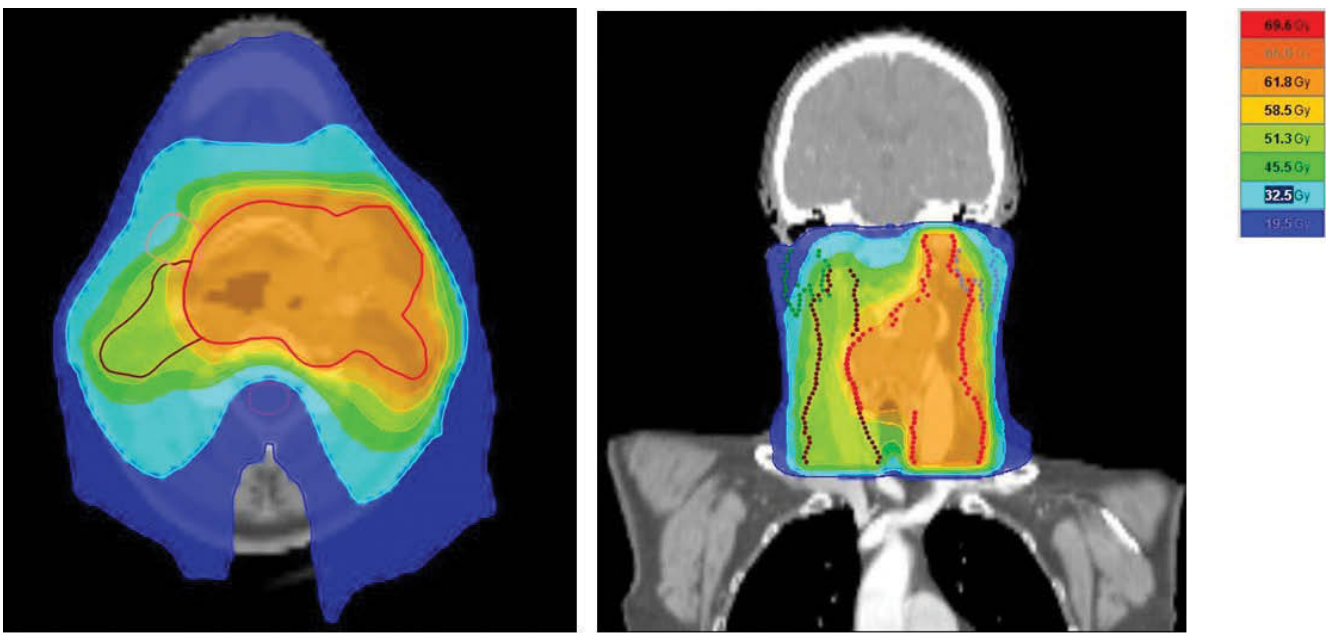

Figure 16.8 Axial and coronal section of an IMRT plan for a patient with T3N2b disease of the left pyriform fossa. The prescription dose (orange) encompasses entire larynx and involved nodal levels. The contralateral at-risk nodal level is treated with a prophylactic dose (green).

function of vocal cords as well as technical expertise and availability of treatment facilities. A multidisciplinary approach should involve surgical, radiation and medical oncology experts as well as speech and language therapists. The patient and caregivers must be counselled about available treatment options. The treatment is based on patient preference and tailored accordingly.

In advanced hypopharyngeal cancers with cord fixity and/or cartilage erosion (T3/T4a), the main issue is treating the disease whilst preserving the laryngeal form and function. In patients with good PS, no comorbidities as well as intact laryngeal framework and function (T1-3N0-2c) the standard of care is concurrent chemotherapy with radiation. In patients with compromised laryngeal framework (T4a) or function, the standard treatment is a total or near-total laryngectomy with a partial or circumferential pharyngectomy along with adjuvant radiation therapy. Lastly, in those patients with intact laryngeal function but exolaryngeal spread through the membranes without cartilage involvement, neoadjuvant chemotherapy with response assessment may be considered for chemoselection for organ preservation.

Surgery for advanced hypopharyngeal cancers

Surgery for hypopharyngeal cancer involves the larynx as well as the hypopharynx. The larynx is usually entirely removed unless the lesion is lateralized. The pharynx is usually resected either partially or circumferentially and most patients will need appropriate reconstruction to restore pharyngeal continuity. Adjuvant radiation / chemoradiation is an essential part of the multimodal therapy for treatment of stage III / IV hypopharyngeal cancers treated surgically.

INDICATIONS

- good general condition
- compromised laryngeal function
- involved laryngeal framework
- salvage surgery following radiation or concurrent chemoradiation.

CONTRAINDICATIONS

- poor general condition
- disease extension
  - Involvement of root neck
  - Prevertebral involvement presents with inability to extend the neck and absence of laryngeal crackle
  - Superior extension into the oropharynx
  - Lateral extension involving carotid artery
- Metastatic disease

Types of surgical procedures

- near-total laryngectomy with partial pharyngectomy
- total laryngectomy with circumferential pharyngectomy
- total laryngo-pharyngo-oesophagectomy (TLPE) with gastric pull-up (GPU).

Near-total laryngectomy with partial pharyngectomy (NTLP)

Voice conservation procedures preserve voice as well as nasal respiration while total laryngectomy sacrifices both functions on the other extreme. The near-total laryngectomy (NTL) falls midway, preserving voice but not nasal respiration.

Indications for NTLP are advanced but lateralized hypopharyngeal cancers where the lesion does not involve the post-cricoid mucosa or the interarytenoid region; the contralateral vocal cord and arytenoid can be preserved and used to form a biological shunt between the trachea and the neopharynx.

This innervated laryngotracheal remnant is fashioned into a tube which, though inadequate to serve as an airway for breathing, is large enough to act as a dynamic shunt by diverting air from the trachea to the pharynx for voice production. The patient therefore has a permanent tracheostome for breathing as in a total laryngectomy which when occluded diverts air through the shunt to produce speech. The innervated dynamic shunt with its sphincteric action protects the airway, preventing aspiration.

The procedure of NTLP offers preservation of excellent lungpowered speech and may be suitable in almost 20% of advanced, operable, pyriform cancers – the most common site amongst hypopharyngeal cancers.

NTL is contraindicated in the following situations:

- Interarytenoid or post-cricoid involvement, which makes preservation of the contralateral arytenoid oncologically unsafe.
- Mucosal involvement of more than one-third the length of the contralateral cord. This does not allow preservation of sufficient laryngeal remnant for shunt formation.
- Prior radiation therapy is a relative contraindication especially if the tissues are oedematous.

Total laryngectomy with partial pharyngeal resection

In hypopharyngeal lesions involving the inter-arytenoid and post-cricoid mucosa, the entire larynx needs to be sacrificed along with the involved pharynx preserving part of the pharynx after adequate resection.

Total laryngectomy with circumferential pharyngeal resection

Indicated in hypopharyngeal lesions involving the post-cricoid mucosa where there is no option of preserving any pharyngeal mucosa. The lesion should however be limited above the level of the cricopharynx ensuring that the cervical stump of oesophagus is normal.

Total laryngo-pharyngo-oesophagectomy (TLPE)

In post-cricoid lesions or hypopharyngeal lesions extending beyond the cricopharynx, an oncological safe margin

requires total laryngopharyngectomy with removal of the entire oesophagus.

RECONSTRUCTION OF PHARYNX FOLLOWING PHARYNGEAL RESECTION

After partial pharyngeal resection, the remnant pharynx is evaluated for mucosal adequacy at the oropharynx, mid-pharynx and the cricopharynx as well as its texture and vitality. If the width is less than 3 cm unstretched or the remnant pharynx is not pliant and oedematous a reconstruction should be considered. The long-term study from Queen Mary Hospital, University of Hong Kong, by Hui et al, showed that a 3 cm unstretched pharyngeal remnant ensures a normal swallow in patients.[90] There are three varieties of defects created:

Partial pharyngeal defects

This requires reconstruction with a pliant tissue similar in thickness of the pharynx. For partial defects, radial artery free flap or anterolateral thigh free flap are suitable. Alternatively, pectoralis major myocutaenous (PMMC) pedicled flap can be used.

Circumferential defects

In our experience, circumferential pharyngeal defects are ideally reconstructed with free jejunal graft. Skin-lined tubed reconstruction, if done, should preferably be a free radial forearm flap. Tubed PMMC is a possible but poor alternative.

Gastric pull-up (GPU)

Following a TLPE, the defect is reconstructed by mobilizing the stomach along with a segment of the duodenum which allows the stomach to be brought into the neck and is sutured to the oropharynx at the fundus. GPU offers a reliable, single-stage vascularized reconstruction with anastomosis in the neck, minimizing the risk of stricture, fistula and post-operative mediastinitis. The GPU is however fraught with higher morbidity in the post-operative period.

MANAGEMENT OF NECK

In stage III and IV either the patient has manifest neck nodes (N1-N3) or has advanced primary (T3/T4) tumour. With manifest neck nodes the surgical plan will usually be bilateral neck dissection levels II–V. In patients with advanced primaries and no neck nodes, the surgical plan will entail bilateral levels II to IV neck dissection.

FUNCTIONAL OUTCOMES

In advanced hypopharyngeal cancers treated surgically, the functional outcomes are related to swallowing and speech. The pharyngeal remnant and the effect of adjuvant radiation will determine the ease of swallow. Generally, patients undergoing primary closure with an adequate pharyngeal width (more than 3 cm unstretched) will experience swallow outcomes close to normal. During neopharynx formation, only mucosal closure vs mucosal and overlying pharyngeal muscle closure has been shown to affect swallowing. Propulsion of the bolus with pharyngeal muscle approximation is more effective while the amount of bolus swallowed is better with only mucosal closure. Thus, during closure the surgeon should ensure that the pharyngeal remnant is adequate and avoid a tight pharyngeal muscle closure. Swallowing is similar in NTLP to TLP with a pharyngeal stenosis rate of 10% caused either by a narrow pharyngeal remnant or radiation-induced stenosis.[91] The pharyngeal reconstruction with a vascularized patch does not alter the function of swallowing and speech in a major way. The only issue remains the amount of functional pharyngeal remnant which can preserve peristalsis. Disordered motility can cause stasis and is more common when the major part of the pharynx is reconstructed.[92] The main concern in gastric pull-up is the gastric emptying. The patient would have to remain upright for fear of regurgitation on lying down after eating. The issue is less with a proper pyloroplasty and most patients have good swallowing albeit with reduced food volume and occasional regurgitation within the first 3 months.

Speech is determined by the pliability of the pharyngo-oesophageal segment. With a remnant pharyngeal mucosa, the speech restoration with tracheo-oesophageal prosthesis is successful in more than 90% of patients. When the laryngeal remnant is preserved as in a NTLP the patients acquires an intelligible, lung-powered speech. Almost every patient will speak following this procedure unless there is a shunt breakdown or stenosis, which is uncommon and is usually technique related, which can be minimized with experience. Results from most published series demonstrate success rates ranging from 74% to 100%.[93–97] Occasionally, a patient may not develop speech or may have to strain while talking. The commonest cause of this is NTL shunt stenosis. This can be overcome by dilatation of the tract using simple gum elastic bougies.

ONCOLOGICAL OUTCOMES

In properly selected cases, the locoregional control rates with near-total laryngectomy are comparable to those with total laryngectomy. In our own series consisting predominantly of T3 / T4 cancers, local recurrence rate is less than 7% with a median survival of 57%.[91] A national analysis of over 1500 patients in the UK showed a 5-year survival of 57% for those treated with pharyngolaryngectomy.[98]

MORBIDITY

The morbidity of surgical treatment in hypopharyngeal cancers is related to the integrity of the neopharynx. Salivary leaks occur more commonly in patients who undergo primary pharyngeal closure for hypopharyngeal cancer surgery compared to those for laryngeal cancers[94]

and may be related to the remnant pharyngeal width. The pharyngeal leak rates are higher in post-irradiated patients, seen in almost 50%. Salvage surgery following concurrent chemoradiation tends to have a higher chance of salivary leak, the incidence rates of which can be reduced by a third using vascularized tissue to reconstruct the defect.[99] In circumferential pharyngo-oesophageal defects, reconstruction with free anterolateral thigh flap seem to have higher success rate (96% vs 93%) compared to free jejunal flap reconstruction, achieving best functional outcome with minimal donor-site morbidity.[94]

The mortality in surgically treated hypopharyngeal cancers is a reality. Nouraei et al have reported the average hospital mortality rate for laryngopharyngectomy around 6% with the gastric pull-up group having the highest incidence at 11%. Those that have had a reconstructive failure tend to have an odds ratio of 6:2 for in-hospital death as well as a worse prognosis.[98]

ADJUVANT THERAPY

Following surgery in advanced stage III and IV hypopharyngeal cancers, adjuvant therapy with either radiation therapy or concurrent chemoradiotherapy is an essential part of the treatment protocols. The factors warranting adjuvant treatment are advanced primary cancer (T3/T4), close- or positive-cut margins, presence of perineural invasion (PNI), lymphovascular embolii (LVE), extension/invasion to adjacent structures like cartilage, muscle, soft tissues, multiple nodal involvement and finally the presence of extra-capsular extension (ECS) in the nodes. There is conclusive evidence for use of concurrent chemotherapy with radiation in cases with positive margins and extra-capsular spread.[100, 101]

Non-surgical organ preservation strategies for advanced hypopharyngeal cancers

Non-surgical organ preservation aims for good locoregional control with function preservation i.e. no aspiration or need for tracheostomy and feeding tubes after completion of treatment. However, careful patient selection is essential to ensure optimal results.

CHEMORADIATION FOR ADVANCED HYPOPHARYNGEAL MALIGNANCIES

The evidence for concomitant chemoradiation in hypopharyngeal cancers comes from the recent update of the MACH-NC with subgroup specific analysis. In the MACH-NC update including 87 trials and 16485 patients, Pignon et al compared locoregional treatment with or without chemotherapy.[102] The hazard ratio of death was 0.88 ($p < 0.0001$) with an absolute benefit for chemotherapy of 4.5% at 5 years and a significant interaction ($p < 0.0001$) between chemotherapy timing (adjuvant, induction or concomitant) and treatment. Concomitant chemotherapy was found to be better than induction chemotherapy. For the 50 concomitant chemoradiation trials, the hazard ratio was 0.81 ($p < 0.0001$) and the absolute benefit was 6.5% at 5 years. The meta-analysis showed benefit for concomitant chemotherapy irrespective of type of radiation (conventional or altered fractionation). The study also concluded that multi-agent chemotherapy did not provide a significant benefit over single-agent cisplatin in the concurrent setting and compared to any other chemotherapeutic agent, platinum-based chemotherapy was significantly efficacious. There was a decreasing effect of chemotherapy with age suggesting that this strategy may be less beneficial in patients over the age of 70 years.[102]

In the MACH-NC comprehensive analysis by tumour site[103] there were 2767 patients with hypopharyngeal cancers. The study suggested that addition of chemotherapy has an absolute 5-year overall survival benefit of 3.9% in the definitive setting with concomitant chemoradiation, both with conventional and altered fractionation.

Non-surgical treatment is used in resectable advanced hypopharyngeal malignancies for organ preservation and when medical comorbidities preclude surgery. Chemoradiation is generally accepted as the gold standard of treatment in advanced laryngeal cancers without frank cartilage erosion. This has been extrapolated to hypopharyngeal cancers despite there being greater risk of both acute and chronic toxicities.[104]

Larynx preservation with concomitant chemoradiation

Chemoradiation scores over surgery with its ability for larynx preservation. However, there have never been any randomized trials comparing chemoradiation vs surgery followed by radiation in hypopharyngeal cancers. The only evidence we have today are single-arm studies, which

TABLE 16.4 MACH-NC UPDATE [Hypopharynx subset] Hazard Ratio of death and 5-year OS

	Timing of chemotherapy			Test of interaction	OS Hazard ratio
	Adjuvant	Neoadjuvant	Concomitant		
HR [95% CI]	1.06 [0.82; 1.38]	0.88 [0.75; 1.02]	0.85 [0.75; 0.96]	$p = 0.31$	*0.88*
5-year abs benefit [CI]	–2.3% [–13.7 9.1]	+5.3% [–0.8; 11.4]	+4% [–1.1; 9.1]		

have shown encouraging results with respect to larynx preservation.

In a study by Huang et al[105] on 33 patients with advanced resectable hypopharyngeal cancers treated with IMRT and concomitant chemotherapy, the laryngeal preservation rate was 67% with a 5-year overall survival (OS) of 44%. A similar study by Liu et al[106] on 27 patients showed laryngeal preservation rates of 63% and 5-year OS rates of 35%. The only randomized controlled trial[107] comparing induction chemotherapy followed by radiotherapy to concomitant chemoradiotherapy for laryngeal preservation in T3M0 pyriform sinus carcinoma, found significantly better laryngeal preservation rate of 92% at 2 years in the concomitant chemoradiation arm as compared to 68% for the induction chemoradiotherapy group.

INDUCTION CHEMOTHERAPY FOR ADVANCED HYPOPHARYNGEAL MALIGNANCIES

When induction chemotherapy is used in conjunction with concurrent chemoradiation in HNSCC, the treatment is referred as sequential chemoradiation. The rationale underlying the use of induction chemotherapy is based on the expectation that drug delivery is better in untreated well-vascularized tumour, and the eradication of micrometastatic disease may be achieved because of high response rate and better tolerance to induction chemotherapy in treatment-naive HNSCC patients.[106]

The approach generally used is to use two to three cycles of induction chemotherapy followed by response assessment. Responders are continued with definitive chemoradiotherapy whereas non-responders are offered surgery. The earliest randomized evidence in favour of induction chemotherapy came from the EORTC 24891 trial[108] conducted in patients with tumours that would require total laryngectomy. This trial randomly allocated patients to induction chemotherapy with cisplatin and 5-florouracil (5-FU) followed by definitive radiation vs primary surgical resection and post-operative radiation. With a median follow-up of 10 years, this trial demonstrated no significant difference in 5- or 10-year OS or progression-free survival.[109] Of note, two-thirds of living patients in the chemoradiotherapy arm were able to retain their larynxes. Thus, PF became the standard induction chemotherapy regime. This is the only randomized controlled study for hypopharyngeal cancer patients and it needs special emphasis that the organ preservation rate in this study was 42% at 3 years with no difference in overall survival.[109]

The only randomized trial comparing induction chemotherapy followed by radiotherapy to concomitant chemoradiotherapy in T3 pyriform cancers showed larynx preservation rates which were lower for the induction arm (68% at 2 years), but there was no difference in the event free survival rates.[107]

The MACH-NC data showed no benefit of multiagent chemotherapy regimes. However, this was a meta-analysis of earlier trials.[102] The later studies evaluated the addition of docetaxel (T) to the backbone of cisplatin and 5FU (PF) to facilitate organ-preservation in locally advanced laryngeal or hypopharyngeal cancers. A randomized French study on 213 patients demonstrated that TPF induction chemotherapy (compared to PF induction) results in superior tumour response rates (80% vs 59%) as assessed by laryngoscopy and CT or MRI.[110] Those with response to induction chemotherapy were treated with organ-preserving (chemo)radiotherapy, while non-responders received laryngectomy and post-operative (chemo)radiation. The higher response rates in the TPF arm allowed for higher rates of laryngeal preservation (70% vs 57% at 3 years), without a detriment in OS (60% at 3 years in both arms). The superiority of TPF was reconfirmed in their long-term follow-up with 10–year larynx preservation at 70.3% vs 46.5% ($p = 0.01$) in the TPF vs PF arm respectively.[111] However, no difference was seen in overall survival, disease-free survival or locoregional control rates between the two arms.

The TAX-324 study utilized similar induction chemotherapy arms (TPF vs PF), followed by concurrent chemoradiotherapy with carboplatin in locoregionally advanced cancers.[112] Five-year survival in the TPF arm was 52% vs 42% receiving PF, while no increased rates of gastric feeding tubes or tracheostomies were noted between groups. A subgroup analysis of larynx and hypopharynx patients demonstrated improved survival in these patients, as well as higher rates of laryngectomy-free survival.

Thus, for advanced hypopharyngeal cancers which have intact laryngeal framework and function, induction chemotherapy (multi-agent TPF) followed by chemoradiation in responders seems to be superior in preservation of larynges and triaging out patients for surgery. Morbidity of the therapy is high and should be kept in mind while selecting a suitable patient for organ preservation.

ALTERED FRACTIONATION FOR ADVANCED HYPOPHARYNGEAL MALIGNANCIES

Another method of organ preservation is by intensification of radiation therapy. Altered fractionation radiotherapy modifies the dosage or fractionation schedules of conventional fractionated radiotherapy. Altered fractionation has been found to improve locoregional control with a potential for organ preservation. A meta-analysis of radiotherapy in carcinomas of the head and neck (MARCH) established the survival benefit of altered fractionation, especially with hyperfractionation having an 8% absolute benefit at 5 years over conventional radiotherapy.[113] A multicentric randomized control trial, comparing accelerated (6 days per week) compared to conventional (5 days per week) showed a 12% 5-year locoregional control advantage.[114] However, there were few hypopharyngeal cancers in most of these studies.

There are a few retrospective series looking at the role of altered fractionation in hypopharyngeal cancers. Niibe et al[115] reported the results of 42 patients with

hypopharyngeal carcinoma who were either inoperable or refused surgery treated with curative intent radiation therapy. Hyperfractionated radiation therapy was used in 23 whilst 19 were treated with conventional fractionation. They found significantly better 3-year local control rates (61.5% vs 18.4%), pharyngolaryngectomy-free-survival rates (64.7% and 5.3%) and a relatively better overall survival rate (69.3% and 31.6%, $p = 0.075$) with hyperfractionated RT with acceptable toxicity. Kawashima et al[116] used a 'chemotherapy enhanced accelerated radiotherapy' regimen to improve control rates in T2–T4 hypopharyngeal cancers; 35 patients received 40 Gy/4 weeks to the entire neck followed by boost RT administering 30 Gy/2 weeks (1.5 Gy twice-daily fractionation). Cisplatin and 5 fluorouracil were administered concomitantly only during the boost RT. They reported encouraging results with overall survival and local control rates at 3 years being 91% and 88% respectively, without significant effects on swallowing.

Salvage surgery after organ preservation

The premise of offering organ preservation is based on the ability to salvage if the treatment does not succeed. This is critical in the counselling of the patient whilst planning treatment.

RESIDUAL LOCAL DISEASE

The hypopharynx is at the highest risk for locoregional and distant failure following standard treatment protocols. Organ preservation strategies for advanced hypopharyngeal cancers are generally applied in Stage III/IVa cancers. However, control rates after primary radiotherapy/chemoradiation are low, with around 30–50% of patients having residual/ local recurrences.[117–119] Most of these patients tend to be unresectable with recurrences involving the prevertebral fascia or carotid artery. When salvageable, the surgery for most cases would be a laryngopharyngectomy with pharyngeal reconstruction.[120–122] In a retrospective study,[119] the successful salvage rate was 17.1% (7/41 patients who recurred locally after radiotherapy). None of the patients who had a primary T4 disease could be successfully salvaged. In a similar study on salvage laryngectomy post-chemoradiation for laryngeal and hypopharyngeal cancers, only 10% of patients with recurrent hypopharyngeal carcinoma underwent salvage surgery.[123]

Salvage laryngopharyngectomies have an increased rate of complications especially pharyngocutaneous fistulae which may occur in up to 50%.[117] Concomitant chemoradiotherapy with radiation doses more than 64 Gy increase this risk considerably. Pharyngocutaneous fistulae in turn increase the incidence of carotid artery blowouts. With a low salvage potential and high rate of complications it is imperative to carefully choose patients for organ preservation, and the surgical team should have a low threshold for using vascularized tissue from non-radiated areas to reconstruct or buttress the pharyngeal repair.

RESIDUAL NECK DISEASE

Limited neck disease (N1) tends to respond well to chemoradiotherapy. Large volume nodal disease (N2 or N3), however, has a poor response despite chemoradiation. In case of palpable or radiologically obvious remnant neck node, salvage neck dissection is done. Generally, a modified neck dissection levels II–V is performed. In case neck nodes are not palpable but picked up on PET-CT scan at 12 weeks in the surveillance scan, a neck dissection is performed on those findings.[124] Larger neck nodes have a reduced salvage potential and increased morbidity and the same caution should be exercised before deciding on organ preservation.

MANAGEMENT OF RECURRENT AND METASTATIC DISEASE

Patients with recurrent disease should be triaged into locoregional and distant metastasis. The management of recurrences depend on recurrent staging, interval between completion of treatment and recurrence (disease-free interval), patient's PS, presence of comorbidities, patient's willingness for further treatment, 'salvageability' potential and durability of control.

Prior treatment has an immense bearing on the salvage treatment. Potential for durable response to treatment improves if surgical salvage is followed by adjuvant radiation/chemoradiation received. In a previously irradiated patient the fields of radiation and the potential for re-irradiation should be discussed prior to salvage surgery.

Many patients with hypopharyngeal cancer develop distant metastases at some point in their clinical course. When this occurs, long-term survival is rare and the treatment intent is palliative in nature. The median overall survival for patients with metastatic head and neck cancer is 6–10 months. Palliative treatment should be planned to improve the remaining quality of life and includes symptom control with appropriate pharmacological interventions, radiation therapy, chemotherapy and best supportive care.

Pain alleviation with narcotic pain medication is invaluable. Palliative radiation therapy is suitable in patients with local pain or bleeding. Palliative chemotherapy can be considered in patients with good PS and disseminated disease. Single-agent cisplatin has been shown to improve overall survival in head and neck cancer patients.[125] Historically, combinations of cytotoxic chemotherapies do not improve survival in comparison to cisplatin alone and are not used routinely. Recent randomized evidence supports the use of a triple drug regimen (cisplatin or carboplatin, 5 fluorouracil and the anti-epidermal growth factor receptor monoclonal antibody cetuximab) in recurrent or metastatic head and neck cancer,[126] with addition of cetuximab to platinum and 5FU significantly improving OS from 7.4 to 10.1 months. However, patients with poor PS should be offered best supportive care and pain medications.

FOLLOW-UP OF PATIENTS

Patients treated for hypopharyngeal cancers should be followed up to check their functional status as well as look out for recurrence. Functional status includes swallowing and speech apart from morbidity related to surgery and radiation therapy.

Follow-up schedule

The standard follow-up schedule is bimonthly for the first 2 years, quarterly in the third year and biannually in the fourth year. From the fifth year, annual check-ups are done with a high index of suspicion for second primary cancers.

Speech

Patients treated with radiation/chemoradiation should undergo periodic speech assessment and therapy to counter the effects of radiation on the vocal cords. Over time the muscle tends to atrophy and the patients are counselled to do regular speech therapy. The speech therapy should be initiated during the treatment itself to inculcate proper vocal 'hygiene' habits in the patients. This includes vocal exercises, vocal naps, hydration and taking care of gastro-oesophageal reflux.

In those rehabilitated with a tracheo-oesophageal prosthesis, careful evaluation for any signs of leakage either through or around the puncture site is carried out. Care of the prosthesis with antifungal application as well as regular cleansing is to be reiterated. This will be further elaborated in the chapter on speech rehabilitation Chapter 34, Speech voice and swallow rehabilitation after chemoradiation.

Swallowing

During radiation/chemoradiation active swallowing and speech therapy is advocated. This must be evaluated at every follow-up appointment. Proactive intervention during the treatment process and continuation thereafter may prevent the fibrosis that sets in which impedes restoration of a normal swallow. Use of saliva substitutes improves swallowing.

A consult with the speech and language pathologist prior to treatment initiation is important. The patients should be counselled to persist with the oral swallowing to reduce the amount of radiation induced fibrosis. On treatment completion the patients are evaluated for signs of aspiration and pharyngeal stenosis which needs dilatation and active therapy.

Dental check-up

Dental check-up for carious teeth and damaged crowns should be done diligently prior to radiation. During follow-up, fluoride gel application is advised regularly to strengthen the enamel and prevent dental carries. Hydration and its importance in preventing halitosis, periodontitis should be impressed on the patients.

Thyroid status

The thyroid gland is either removed partially or completely during surgery and/or radiated following surgery. In either case the patient may turn hypothyroid following treatment for hypopharyngeal cancer. The thyroid function tests should be done when symptomatic or routinely at 6 months following completion of radiation. Thyroxine replacement is started if hypothyroidism sets in and replacement is based on body weight at 1–2 mcg per kg.

Disease surveillance

The patients should be monitored for second primary cancers in the upper aerodigestive tract which are seen in up to 50% of patients. The risk of new cancer development increases by 1% annually. The patients who continue to abuse tobacco and alcohol have a 15–20% increased recurrence risk and should be counselled to desist.

PET-CT scan should be done between 10 and 12 weeks for optimum benefit following radiation in those treated with organ preservation. The negative predictive value of PET-CT is above 95% and is an important indicator of disease control.

SUMMARY

Hypopharyngeal cancer is a high-risk cancer. There are fewer barriers to spread of disease and a good lymphatic network yields a high incidence of occult nodal metastasis. The chance of synchronous tumours is 15% and distant disease at presentation is known. The long-term overall survival in stage III & IV cancers is low. Treatment of hypopharyngeal cancers is fairly morbid affecting speech and swallowing and is requires multidisciplinary planning. Careful evaluation of laryngeal and pharyngeal function in treatment planning is of paramount importance. Organ preservation in advanced hypopharyngeal cancers requires careful case selection. Surgery with adjuvant therapy still remains the gold standard in the management of advanced hypopharyngeal cancers.

KEY POINTS

- Accurate staging is essential. Workup should include evaluation for synchronous primaries and distant metastasis.
- Laryngeal function should be accurately evaluated prior to treatment especially while considering organ preservation.
- Radiation therapy is recommended for Stage I and II disease.
- Multimodality treatment is recommended for Stage III and IV disease.
- The overall 5-year, tumour-specific survival is less than 30%, although the survival of treated patients rises to 50%.

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CHAPTER 17

NECK METASTASES FROM AN UNKNOWN PRIMARY

Ricard Simo, Jean-Pierre Jeannon and Maria Teresa Guerrero Urbano

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SEARCH STRATEGY

Data in this chapter may be updated by a Medline search as well as the websites Cancerlit and Cancer Net using the keywords: neck mass, carcinoma of occult primary (COP), carcinoma of unknown primary (CUP), head and neck neoplasm, imaging, and focusing on diagnosis, surgery and management. The evidence in this chapter is mainly levels 3–4 with some level 2 evidence. The clinical recommendations are predominantly B and C.

INTRODUCTION

Head and neck squamous cell carcinoma (HNSCC) that presents as carcinoma of unknown primary (CUP) represents a difficult challenge for the practising clinician. With improvements in diagnostic techniques such as cross-sectional imaging, molecular diagnostics, robotics and positron emission tomography (PET) scanning, clinicians are now able to identify a higher proportion of primary sites in patients presenting with CUP than before. The most common presentation of CUP in the head and neck is in the context of human papillomavirus (HPV)-associated oropharynx (HPV+OPSCC) carcinoma. As the year-on-year numbers of HPV+OPSCC are increasing in the developed world, it is likely therefore that the incidence of CUP is also increasing.[1–3]

DEFINITION AND HISTORICAL BACKGROUND

The term carcinoma of unknown primary (CUP) represents a heterogeneous disease entity characterized by the presence of clinically overt metastatic disease in the absence of a clinically or radiologically obvious primary tumour. In the head and neck, the definition of a true unknown or occult primary carcinoma is the presentation of metastatic neck lymphadenopathy without the development or manifestation of an index primary tumour within a subsequent 5-year period.

CUP is diagnosed in a patient who presents with biopsy-proven squamous cell carcinoma (SCC) in one or more cervical lymph nodes and in the absence of an obvious primary tumour despite rigorous clinical examination, appropriate cross-sectional imaging and examination under anaesthesia including an ipsilateral tonsillectomy and biopsy of tongue base mucosa (or formal mucosectomy) +/– biopsy of the mucosa of the post nasal space and/or ipsilateral piriform fossa.

It is important to distinguish between true CUP cases in which a primary site tumour never becomes evident and the case where, on initial presentation, a primary tumour is present but remains undetected.

In the latter case, it is presumed that there has been early metastasis from a small primary tumour following which the growth of the cervical metastasis has proceeded at a considerably faster rate than that of the primary tumour. It is inevitable that, left untreated, the primary tumour would eventually become clinically evident. However, as will be seen later, the sites at highest risk of harbouring a

primary tumour are often treated in any case such that the primary tumour never becomes clinically evident.

It follows therefore, that quantification of the true rate of CUPs is not possible with any accuracy.

One of the first explanations of CUP was suggested by Volkmann in 1882 and widely accepted until the 1940s. He believed that the neck mass resulted from the degeneration of a 'branchiogenic cyst' into carcinoma. In 1940, Martin and Morfit revisited this hypothesis in a study of 55 CUP patients; as only eight met Volkmann's criteria, this theory was dismissed.[4–9] Since then several theories have been proposed in an attempt to explain this clinical phenomenon.

Two hypotheses currently predominate, although neither are proved. In the first hypothesis proposed, as explained above, the microscopic primary tumour lies undetected in the mucosal folds of Waldeyer's ring and is too small to be detected by conventional diagnostic methods and is ultimately successfully treated either by design or coincidental (by inclusion in radiation fields designed primarily to treat the neck).

The second hypothesis, which attempts to explain the existence of 'true' CUPs, supposes that the primary tumour is removed by the patient`s innate or adaptive immune system, but not before early metastasis to the cervical lymph nodes has occurred with subsequent evasion of the host immune response.[10–13]

INCIDENCE

The incidence of CUP in HNSCC has reduced significantly over the last two decades (**Table 17.1**). In the 1970s and early 1980s, prior to the universal availability of cross-sectional imaging, the incidence ranged between 10% and 30%. Many of these historical cases may have been incorrectly diagnosed as CUP as they represented distant metastases from lung and abdominal primaries.[14]

The incidence reported in the literature subsequently plateaued over the last decade to around 5% of HNSCC due to standardized diagnostic protocols.[15–28] Our own single-centre experience at Guy's & St Thomas' NHS Trust has also seen a reduction in the incidence of CUP over the last 10 years from 8% to 4% of new HNSCC cases.[29] It is increasingly recognized that high-risk HPV related HNSCC tends to present with regional disease and clinically unrecognized primary focus, and most patients with CUP presentation will have a primary site in the oropharynx.

NOMENCLATURE

The staging of head and neck cancer is dealt with in detail in Chapter 4, Staging of head and neck cancer However, recent changes to the TNM staging system published in the American Joint Committee on Cancer (AJCC) 8th edition Cancer Staging Manual and the Union for International Cancer Control (UICC) included changes which involve the staging of CUP.

A T0 category is no longer assigned to p16 – OPSCC and other non-HR HPV cancers e.g. larynx, oral cavity and hypopharynx. This is because, in these tumours an exact primary site is, by definition, unable to be established. In contrast, cytology specimens following fine-needle aspiration cytology (FNAC) of an enlarged lymph node in which the presence of metastatic carcinoma is confirmed can be subjected to testing for HPV and Epstein–Barr virus (EBV) status.

It is considered that demonstration of HPV or EBV status safely allows the primary site to be determined as oropharynx or nasopharynx respectively and therefore, classification systems for p16 + OPSCC and nasopharynx maintain T0 categories (as does salivary gland as primary site can be determined on cytological findings). The molecular biological and pathological aspects are discussed in Chapters 6, Introducing microbiology of head and neck cancer and 26, Pathology of head and neck malignancies respectively. The management of HR HPV oropharyngeal cancer can be found in Chapter 13, Oropharyngeal tumours.

EVALUATION AND DIAGNOSIS

Clinical assessment

Patients presenting with metastatic lymphadenopathy with an occult primary should undergo a structured diagnostic workup, as recommended by evidence-based guidelines. A thorough history is essential. A history of excessive alcohol consumption and heavy smoking may suggest a primary tumour outside the nasopharynx, while a history of multiple sexual partners and orogenital contact may suggest a primary tumour within the oropharynx.[14] Clinical examination should include fibre-optic nasolaryngoscopy with special attention to sites where a small primary focus can be missed, such as the nasopharynx, tongue base, the infrahyoid epiglottis and the pyriform sinus. The site of the node is an indicator of the primary site. For instance, level I nodes are almost never seen with nasopharyngeal primaries

TABLE 17.1 Treatment recommendations by ENT-UK Multidisciplinary Treatment Guidelines (2016)

Stage	Surgery	Radiotherapy	Chemotherapy
T0N1M0 (No ECS)	SND or MRND	No unless for mucosal sites	No
T0N1M0 (ECS)	SND or MRND	Yes to neck	Should be considered
T0N2M0	SND or MRND	Yes – ipsilateral but contralateral should be considered	Should be considered
T0N3M0	MRND or RND	Yes – ipsilateral but contralateral should be considered	Should be considered

and level V nodes never with laryngeal cancer. Based on epidemiological data and lymph node distribution, nomograms have been created to predict the primary site.[30]

Novel endoscopic techniques, used in the clinic setting, have shown use in this scenario. Narrow band imaging (NBI) is based on the modification of the standard white light endoscope in which white light is transmitted through optical filters absorbing all but two wavelengths; one band centred at 415 nm and another at 540 nm. The former wavelength penetrates the superficial mucosa and highlights submucosal capillaries as a brown colour while the latter penetrates through the submucosal layer and identifies prominent vessels as cyan in colour. As SCCs arising from the upper aerodigestive tract mucosa are accompanied by neoangiogenesis, NBI identifies neoplastic tissue at an earlier stage than conventional endoscopy. A meta-analysis[31] of four studies where NBI was performed on 115 patients with CUP demonstrated a high level of diagnostic accuracy(sensitivity (74.1%; 95% confidence interval [CI] 52.5%–100%) and specificity (94.1%; 95% CI 5 23.7% –100%)).

This should be followed by cross–sectional imaging such as multi-planar computed tomography (CT) or and magnetic resonance imaging (MRI) and FDG PET-CT before the patient is subject to an assessment under general anaesthesia.[32] If the primary is not identified following the above sequence of investigations, then the patient should undergo pandendoscopy under general anaesthesia which should include biopsies based on the results of the core biopsy and imaging. Sites to be sampled include the nasopharynx, tongue base and ipsilateral tonsillectomy.[33] Using this protocol, most CUP cases turn out to be either tonsil or tongue base primary cancers.[14, 29]

RIGID ENDOSCOPY GUIDED BIOPSY OF THE NASOPHARYNX

Blind biopsies of the nasopharynx have proven to be unsatisfactory as they often provide a poor yield of primary site diagnosis.[30] It is therefore recommended that biopsies on this site should be guided using rigid telescopes,[14] especially where abnormalities have been noted on imaging. In instances where high-resolution imaging does not identify pathology, even telescope-guided biopsies are unlikely to pick up a malignant focus.

BILATERAL TONSILLECTOMY

There is evidence from selected series that bilateral tonsillectomy should be employed as the primary resides in the contralateral tonsil in up to 10% of cases.[34–36] In the high-risk HPV era, there is greater recognition that these tumours can be multifocal at presentation,[37] providing further basis for a bilateral tonsillectomy (**Figure 17.1**). It has been suggested that bilateral tonsillectomy could reduce the need for bilateral irradiation to the neck, thus leading to reduced morbidity. In patients who have undergone previous tonsillectomy but they have tonsillar remnants, the search for the primary should also include the excision of the remnants as primary tumours can be found within them.[38, 39]

TONGUE BASE BIOPSIES

Blind biopsies of the base of tongue (BOT) are often unsatisfactory as occult carcinomas rarely arise from the mucosal surface. It is therefore advisable to target the deep tissue of the BOT. The superior manoeuvrability and access provided by transoral robotic techniques have led to the design of the procedure called tongue base mucosectomy (TBM, **Figures 17.2** and **17.3**). This procedure samples the entire tongue base mucosa and has been shown to identify a primary site in over 50% of patients who are PET negative and have no primary site in the tonsil. Interestingly, around 10% can be contralateral foci. However, the morbidity of this procedure cannot be underestimated, with the risk of bleeding, need for tube feeding and the very small risk of pharyngeal stenosis.[40, 41]

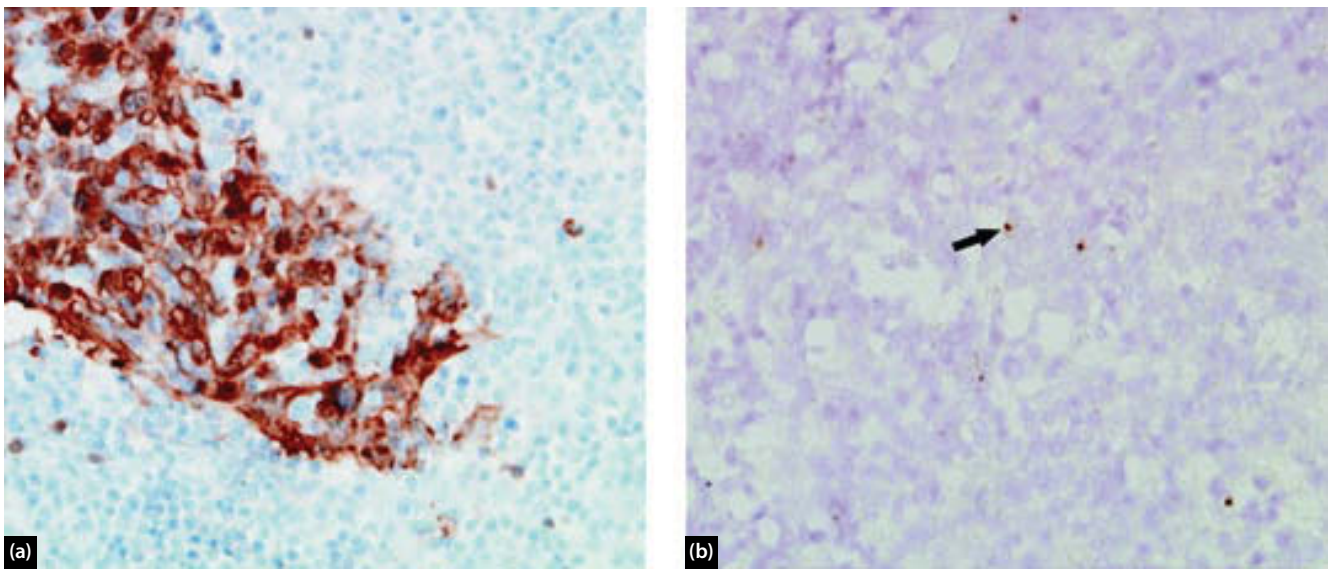

Figure 17.1 Photomicrograph showing immunohistochemistry positivity to p16 in a lymph node of a patient with metastatic HNSCC of unknown primary suggesting a tonsil origin. (a) P16 positivity in the tonsil **(b)** identified malignant cells in the tonsil.

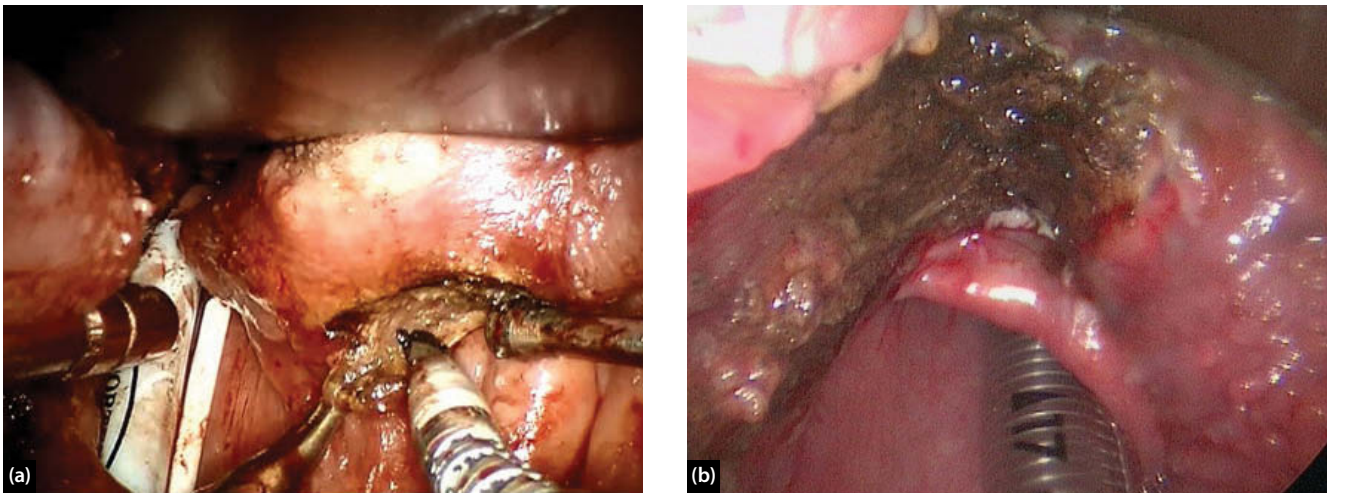

Figure 17.2 (a) A robotic tongue base mucosectomy in progress and **(b)** completed procedure.

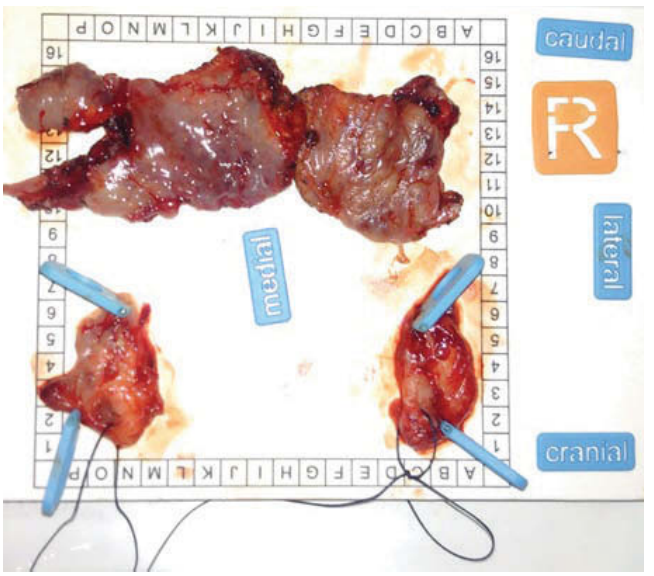

Figure 17.3 A bilateral tonsillectomy and robotic tongue base mucosectomy specimen orientated and mounted for pathological examination.

POSITRON EMISSION TOMOGRAPHY (PET) SCANNING

Fluorodeoxyglucose[18] (G) positron emission tomography (FDG-PET) scanning is now a key modality in the evaluation of the unknown primary. It is combined with a CT scan to provide anatomical localization of the avid lesion (fusion or co-localized PET scanning).

A recent meta-analysis of FDG-PET-CT from the Netherlands has reported data from 11 studies including 433 patients with CUP. Overall primary detection rate was 37%, with equal sensitivity and specificity of 84%. A negative PET-CT result does not preclude the requirement for panendoscopy and multiple site biopsies.[42, 43] Other studies have identified the sensitivity and specificity of PET scanning in identifying the primary in HNSCC to be as high as 87% and 92% respectively.[32–39]

It should be noted that this investigation is only useful if it is performed before the panendoscopy and biopsies, as the post-biopsy inflammatory response may increase the uptake of the FDG tracer, causing a false positive result (**Figure 17.4**).

NICE RECOMMENDATIONS

The pathways for assessment of neck lumps vary across different healthcare settings. Based on low- to high-quality evidence from retrospective studies, an original systematic review, meta-analysis of diagnostic parameters and the experience and opinion of an expert panel, the National Institute for Health and Care Excellence (NICE) made the following recommendations for people with a neck lump that is thought to arise from a head and neck cancer[44] (NICE terminology uses 'offer' to reflect a strong recommendation and 'consider' for a recommendation where the evidence of benefit is less certain):

1. Consider adding ultrasound guidance to fine-needle aspiration cytology or core biopsy.
2. Consider having a cytopathologist or a biomedical scientist to assess the adequacy of the cytology sample.
3. Consider a FDG PET-CT scan as the first investigation to detect the primary site.
4. Consider using NBI (in clinic or during general anaesthetic assessment) in cases where PET-CT has filed to identify a primary site.
5. Offer surgical diagnostic assessment if the FDG PET-CT does not identify a primary site, including guided biopsies, tonsillectomy and TBM.

These have been summarized in an algorithmic fashion in **Figure 17.5**.

CLINICAL MANAGEMENT

Management of CUP continues to generate controversy in multidisciplinary tumour board and scientific meetings.

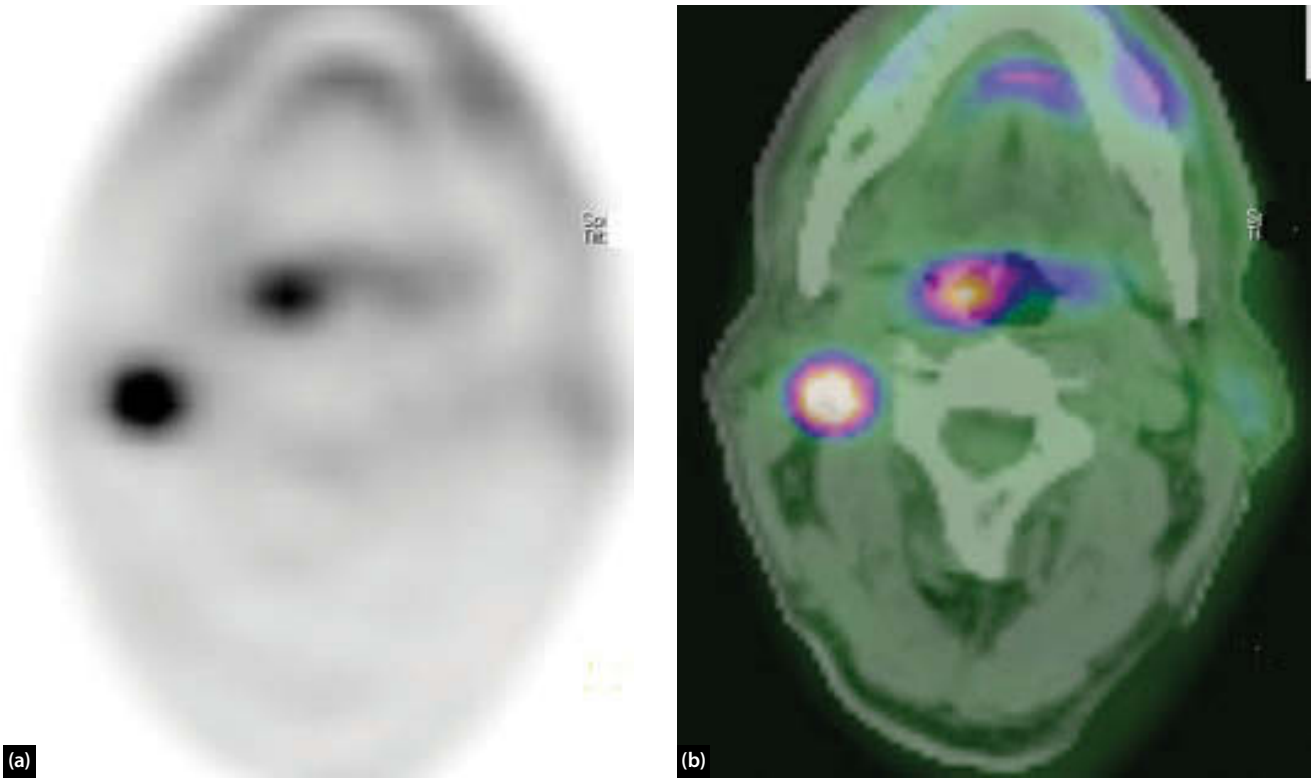

Figure 17.4 FDG-PET-CT scan demonstrating uptake tracer in the right oropharynx in a patient presenting with metastatic SCC of the right neck performed before panendoscopy and biopsy.

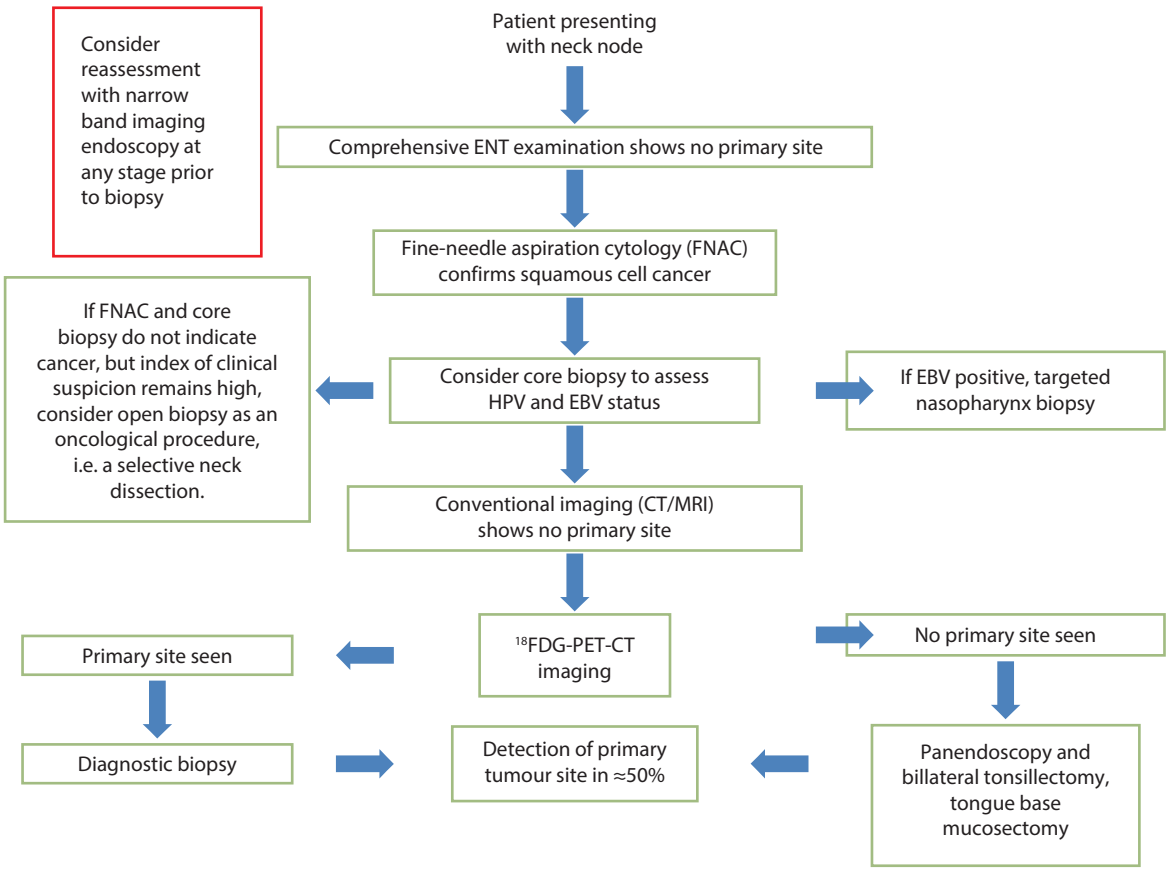

Figure 17.5 Suggested algorithm for the management of the unknown primary.

CUP management can be organized into the treatment of early disease (N1 with no extracapsular spread) and advanced disease (extracapsular spread, N2 and N3).[42, 43] In early disease, single-modality therapy can be considered in the form of neck dissection alone or radiotherapy alone. Radiation therapy alone has been reported for small N1 stage disease with some success and can be considered in patients with comorbidities that can pose a high surgical risk.[40] Similarly, some authors have adopted neck dissection surgery alone without radiotherapy for N1 neck disease with a 'watch & wait' approach to the primary.[41] Advanced cases require combined modality therapy.[45–47] In the absence of high-level evidence, management is largely based on institutional protocols.

Surgical management of the neck

Traditionally, either radical neck dissection or modified radical neck dissections have been employed in the management of CUP. Selective neck dissection has been suggested as a valid option for patients with N2a and N2b disease as the risk of metastases in levels I and V has proven to be rare in patients with CUP unless they present with N3 neck disease.[29, 44]

Traditionally, most units favour neck dissection upfront followed by either RT or chemoradiotherapy (CRT) as indicated. This allows adequate pathological staging of the neck and therefore tailoring treatment accordingly. There is also an advantage of performing surgery in a non-irradiated neck and therefore minimizing morbidity. This approach could potentially cause a treatment delay if any unexpected complications from the surgery occur. Primary RT or CRT will reduce the need for but may render surgery difficult and with an increased risk of complications.

However, recent randomized trials[48] have reported that PET-CT-guided active surveillance after radical CRT showed similar survival outcomes to upfront neck dissection followed by CRT and lead to considerably fewer NDs, fewer complications and lower costs. Although this is in the setting of the known primary, the data is robust enough to warrant a re-examination of current approach for primary surgery in CUP, especially when a firm diagnosis of the neck lump can be established by non-surgical means.[45, 46]

Management of the violated neck

In the past many patients underwent excisional and incisional biopsies as first-line diagnosis. Earlier reports identified poor prognosis in these patients, which has been attributed to inadequate definitive treatment and advanced stage at presentation. With current, centralized, multidisciplilnary team (MDT) driven practices, smaller numbers of patients with lateral neck masses undergo open surgical interventions for diagnosis, primarily due to non-diagnostic FNAC or owing to suspicion of non-SCC pathology such as lymphoma. In the era of adequate surgical management of the neck and good (chemo)radiation practices, open cervical biopsy does not signify a poorer prognosis provided adequate and timely treatment is given.[49] A high proportion of HPV positive oropharyngeal tumours may also explain the favourable outcomes observed.[50] The treatment of the violated neck can be upfront surgery or CRT followed by PET-CT surveillance and surgery as needed.

Branchial cyst carcinoma

The evidence for the existence of branchial cyst or branchiogenic carcinoma is tenuous. Many reported series have failed to meet the criteria set by Hayes Martin and in many cases elective tonsillectomies were not performed. Many patients with CUP may present with lateral neck cystic masses mimicking branchial cysts. There is enough evidence to recommend that all patients over the age of 35 years with lateral cystic masses must be presumed to have cancer until proven otherwise. The authors recommend that these people should be entered into a CUP investigation protocol even if the FNAC is not suggestive of metastatic SCC.[51]

Radiation therapy to the neck and the putative primary site

The external beam radiotherapy (EBRT) fields recommended remains controversial, with some centres offering unilateral radiation to the neck and ipsilateral likely primary sites, whilst others propose bilateral neck treatment, so-called 'total mucosal irradiation'.

Results for bilateral neck irradiation tend to show improved local control rates and disease-free survival compared to unilateral neck treatment. The improvement on overall survival however is not always seen.[43, 45–50]

Unfortunately, the superior survival results seen with bilateral EBRT are at the expense of increased morbidity in terms of pain, xerostomia and long-term dysphagia with increased feeding tube dependence.[46]

Intensity-modulated radiotherapy treatment (IMRT) with bilateral neck radiation has the potential for reduced acute and late toxicity as the parotid glands may be spared, with robust data to suggest that IMRT significantly reduces morbidity.[52, 48] IMRT is currently the standard of care for head and neck cancers in several countries. For CUP patients receiving total mucosal radiation, IMRT appears to provide improved radiation coverage of the mucosa including the nasopharynx with significant reduction of dose to the parotid gland contralateral to the involved neck and therefore reducing the risk of severe xerostomia.[53]

RECOMMENDED TREATMENTS[47, 54]

bcT0N1M0

cT0N1M0 WITHOUT ENE FOUND ON HISTOPATHOLOGICAL OR RADIOLOGICAL STUDIES

Patients can be treated with single-modality treatment either with selective neck dissection or involved field

radiotherapy alone. If treated surgically, the upper aerodigestive tract mucosa should be carefully inspected during surveillance visits.

PT1N0M0 WITH ENE

Patients should be treated with post-operative RT if ENE is identified.

T0N2M0 AND T0N3M0

Patients should be treated with primary CRT followed by PET-CT guided surveillance or combined modality treatment including neck dissection followed by RT or CRT.

TREATMENT OUTCOMES

Most series show improved overall and disease-free survival with combined modality treatment. Survival results are dependent upon the N stage at presentation with worsening outcome observed with increased stage. The outcome and survival of patients with CUP has been variable as the published series are mainly retrospective and represent diverse patient populations. We would however expect a 5-year survival of between 70% and 100% for N1 stage cancers and 30% and 60% for stage N3.

The overall 5-year survival for all stages of HNSCC with unknown primary site would be in the range of 52% and 75%.[39–49] A 10-year single-centre uncontrolled retrospective case series of 25 patients with complete records, from the authors' institution, showed an excellent overall survival for N1 disease of 100% and a 60% survival for patients with N2 and N3 neck disease.[29] (**Figure 17.6**)

In a recent series of patients with CUP treated with IMRT by the Memorial Sloan Kettering Cancer Center showed 2-year regional progression-free survival, distant metastases-free survival and overall survival of 90%, 90% and 85% respectively.[55]

PATTERNS OF FAILURE

The pattern of failure largely depends on the initial treatment protocol. If EBRT is used, disease recurrence is usually in the neck and in form of distant metastasis. Recurrent disease is often difficult to diagnose and it often shows extracapsular spread and presents in advanced stages. FDG-PET-CT scan is probably the best method of detection and diagnosis of recurrences. Distant metastases often occur within a year of treatment completion and are most common in the lung.[51, 52] The incidence of recurrence in the potential primary sites is extremely variable and may occur from 0% to 66%. It occurs mainly in those patients treated initially with surgery alone. The emergence of a primary tumour often occurs within the first 24 months and usually presents in the oral cavity, oropharynx and nasopharynx.[53]

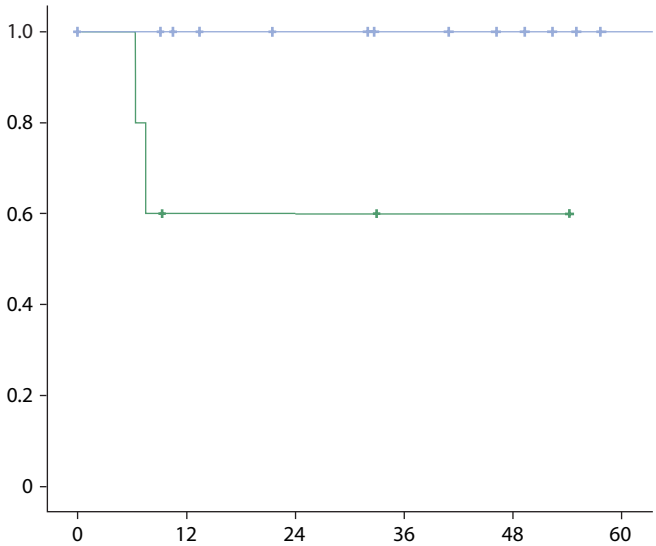

Figure 17.6 Kaplan – Meier Survival Curve for Guy's & St Thomas' series of patients with occult primary carcinoma of the head & neck *n* = 25 (2000 to 2011).

CONCLUSION

The unknown primary in HNSCC is becoming an increasingly rare entity due to better diagnostic protocols and now accounts for fewer than 5% of cases. However, the raw numbers may be on the increase owing to the higher number of HPV-positive cancers. The diagnostic workup should include panendoscopy, bilateral tonsillectomy, biopsies of nasopharynx, tongue base and any other potential suspicious lesions in the upper aerodigestive tract. Investigations should employ cross-sectional imaging CT and or MRI as well as PET-CT imaging; the latter must be performed before the biopsies are taken. Recent modalities being used in the clinical and operative setting allow for a higher primary pickup rate. Most of these cases identify the primary in the oropharynx.

Treatment of CUP should be based on the stage of the disease process, with single modality sufficing for patients with early stage disease. A combination of neck dissection and EBRT may be needed for patients with advanced disease. Bilateral neck irradiation increases overall and disease-free survival at the expense of increased morbidity.

Molecular analysis of the metastatic cervical neck nodes can potentially locate previously occult oropharyngeal or nasopharyngeal primaries.

The survival outcomes are generally good for early and late-stage disease but whether less intensive or single-modality therapy could be adequate in patients who are HPV-positive is yet to be determined.

BEST CLINICAL PRACTICE

- ✓ There is no level 1 evidence for guidance in the management of CUP. Data are at best level 2.
- ✓ PET-CT has shown to have a key rode in the management of patients with CUP and should precede multiple biopsies.
- ✓ Primary surgical management of the neck is preferred to radiotherapy in patients with operable disease.
- ✓ Post-operative selective or total mucosal radiotherapy is indicated for most patients with advanced operable disease.
- ✓ Strategies for the use of new treatment technologies, IMRT and modified radiation fractionation, are largely based on extrapolation of data accumulated for the treatment of known sites of HNSCC.

FUTURE RESEARCH

The management of CUP remains controversial. With the current lack of adequate randomized controlled clinical trials and the decreasing incidence due to improved diagnostic tools, the management of patients with CUP will continue to be challenging.

Most of the current evidence is provided by retrospective single institution studies. With increasing data to suggest that HPV related cancers can be multifocal, further work is needed to define this problem better.

Several questions in the aetiology and management of CUP remain unresolved. These include:

- ➤ Is definitive neck dissection sufficient for patients with N1, N2a and selected N2b disease, avoiding the need for elective total mucosal irradiation?
- ➤ Should definitive RT or CRT should be offered as a primary modality of treatment with salvage neck dissection for persistent disease?
- ➤ Which extent of neck dissection patients should have for each stage?
- ➤ What are the optimal fields for elective irradiation? Ipsilateral, versus bilateral vs total mucosal unilateral or bilateral irradiation.

KEY POINTS

- CUP is an increasingly rare clinical scenario and accounts for only up to 5% of patients with head and neck malignancy.
- Involvement of nodal levels I to IV is almost exclusively associated with occult upper aerodigestive tract primary SCC with level II being the most common site
- Patients should be evaluated with CT, MRI or FDG-PET-CT prior to biopsy in order to guide biopsy site and to avoid imaging artefacts or false positive results with PET-CT.
- FDG-PET-CT has now a clear role on the management of CUP and should be employed whenever possible.
- The only tumour marker of clinical value is Epstein–Barr virus serology as will indicate origin from the nasopharynx. HPV16 status can be determined in tumour cells aspirated from the necks of patients with metastatic HNSCC and its presence is a reliable indicator of origin from the oropharynx.
- Bilateral tonsillectomy may be recommended as diagnostic tool in the evaluation of CUP. Transoral laser and transoral robotic mucosectomies of the tongue base have showed promising results in detecting primary tumours at this site.
- Definitive neck dissection should be performed in all patients with CUP. The extent of the neck dissection requires further evaluation especially on those patients with N1, N2a and limited N2b disease where selective neck dissection could be considered.
- Total mucosal irradiation has demonstrated a reduction in primary site recurrence without any improvement in overall survival. Associated mucositis and xerostomia rates are high.
- Radiotherapy-related morbidity can be reduced if selective mucosal irradiation is undertaken, most commonly by exclusion of nasopharynx especially in patients presenting with II to IV nodal disease.
- IMRT should be considered as the optimal technique for radiation dose delivery.
- For total mucosal irradiation, a dose of 50 Gy in 25 daily fractions, five fractions per week is sufficient for control of occult primary disease.
- Nodal stage is the most important risk factor for local recurrence.
- CRT in patients with CUP should be considered in N3 disease and in those patients with definitive ECS or when resection margins are positive for example around the common carotid artery.

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CHAPTER 18

METASTATIC NECK DISEASE

Vinidh Paleri and James O'Hara

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SEARCH STRATEGY

Data in this chapter may be updated by a search on Pubmed and Medline using the keywords: neck nodes, cervical lymphadenopathy, metastatic lymphadenopathy, neck dissection, occult neck metastases, neck levels and radiation therapy to the neck.

INTRODUCTION

One of the most important prognostic factors in head and neck cancer is the presence or absence, level and size of metastatic neck disease. Many tumours of the head and neck will at some stage metastasize to lymph nodes and a number of factors control the natural history and spread of disease.

Several controversies exist about the management of malignant neck disease, with varying practices on choice, timing and combination of treatment modalities. This is primarily due to the paucity of high-level evidence to many treatment paradigms, but this trend has been reversed with randomized controlled trials and systematic reviews published more recently. However, many organizations have generated guidelines following rigorous evidence gathering exercises, suggesting best management practices based on available evidence in many countries.

This chapter identifies the evidence base and discusses the principles of management of metastatic head and neck squamous cell carcinoma (HNSCC) at initial presentation, residual and recurrent neck disease. It also outlines major clinical controversies regarding the management of the neck in relation to when to treat, how much to treat and which modality to use. It reviews the various rationales for assessment as well as methods for elective and therapeutic treatment and focuses on quality-of-life (QOL) issues. The management of tumours other than HNSCC (i.e. salivary gland and thyroid tumours) are not covered in this chapter.

CLINICAL IMPLICATIONS OF METASTASES

The presence of regional lymph node metastases acts as an indicator of the ability of the primary tumour to metastasize locally and to distant sites, rather than acting as an instigator of distant metastases on their own. This is because lymph node involvement indicates a host response which is permissive for the development of metastases, not only in the regional lymph nodes but also to distant sites. (The molecular mechanisms that promote or prevent metastases is discussed in greater detail in Chapter 6, Introducing the molecular biology of head and neck cancer.) Therefore, the degree of lymph node involvement should be regarded as an indirect index of the systemic tumour burden. Elective removal of regional lymph nodes

serves as a staging procedure to ascertain whether or not metastatic disease is present and to identify high-risk patients who might benefit from systemic adjuvant therapy, but is not expected to diminish the metastatic potential. Akin to breast cancer, tumour-free survival depends more on the biology of the tumour present at the operation rather than at the extent of surgery. This explains why patients with metastatic lymph nodes in HNSCC have a significantly reduced chance of survival when compared with those who have no lymph node metastases.[1]

It has long been recognized that systemic spread can occur early in many solid tumours and this includes HNSCC. Traditional teaching has been to offer wide margin radical surgery to the neck, with the premise that patients who have a large number of occult positive nodes achieve better survival since these nodes are discovered earlier. This philosophy is now being questioned as locoregional disease can be cured with locoregional treatments in a greater proportion of patients, who are now living longer only to die more frequently of second primaries or distant metastases. Overall survival has not changed.

It becomes clear from the above discussion that the spread of HNSCC to the regional lymph nodes indicates an aggressive tumour where the tumour–host balance has swung in favour of the tumour. While there are structural and immunobiological mechanisms that may affect tumour lysis within the lymph node itself, in a certain proportion of cases, systemic spread occurs early on. This can take place by lymphatic or haematological routes. These processes of spread and tumour arrest can be affected by previous treatment. As the systemic immunosuppressive effects of multimodality head and neck cancer therapy are taken into consideration, both the number and the complexity of modalities that are used become ever more important.

NECK LEVELS

It is useful to introduce the concept of neck levels here. The Memorial Sloan-Kettering Hospital published, in 1981, a number of levels or regions within the neck which contain groups of lymph nodes representing the first echelon sites for metastases from head and neck primary sites.[2] These levels have been widely accepted and currently six neck levels are recognized, with level VII being outside the neck and referring to the chain of paratracheal nodes below the suprasternal notch to the level of the innominate artery. These neck node levels (**Figure 18.1**) along with their respective boundaries are described in **Table 18.1**.[3] Levels I, II and V can be further subdivided into (a) and (b). These subdivisions were introduced to recognize certain areas in the neck that have a biological significance independent of the larger zone that they lie in. For instance, Level Ia is rarely involved in malignant processes excluding the lip, anterior floor of mouth and midface. The prognostic significance of level Vb involvement is grave and thus merits the subdivision. The rationale behind subdivision of level II is discussed in 'Elective surgery' below.

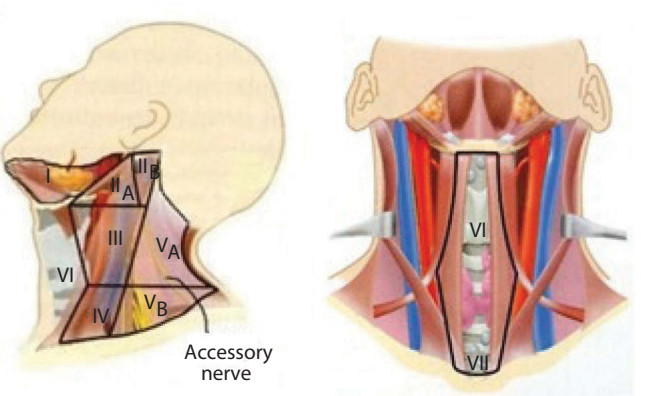

Figure 18.1 The lymph node levels of the neck.

NECK DISSECTION TERMINOLOGY

Standardized neck dissection terminology that was first produced by the American Academy of Otolaryngology and Head and Neck Surgery in 1991 has been updated by the Committee for Neck Dissection Classification of the American Head and Neck Society in 2002 and is widely used (**Table 18.2** and **Figure 18.2**). There is an increasing trend to divide neck dissections into two broad types with subdivisions: comprehensive (removal of levels I–V) and selective (SND) (less than five levels).

The previous division of SND into named subtypes has been superceded by recommendations that the levels or sublevels removed during SND be precisely stated in the operation notes.[4] The term elective neck dissection (END) is used to describe any type of neck dissection that is performed on the clinically and radiologically negative neck (cN0, see below). However, a neck dissection may not fall into one of these standard types, especially in the salvage setting. Recognizing that the current neck dissection terminology will not be appropriate in several post-treatment scenarios, the International Head and Neck Scientific Group has proposed a new classification system for neck dissections.[5]

REGION SPECIFIC LYMPHATIC DRAINAGE

There are approximately 150 lymph nodes on either side of the neck. The normal range in size is from 3 mm to 3 cm but most nodes are less than a centimetre. Within the upper deep cervical nodes in level II, the largest node is often called the jugulo-digastric node and is situated within the triangle formed by the internal jugular vein, facial vein and posterior belly of the digastric muscle. It is important because it receives lymph from a wide area which includes the submandibular region, the oropharynx and oral cavity. The jugulo-omohyoid nodes are situated at the junction between the middle and lower cervical group (low level III/high level IV) where the omohyoid muscle crosses the internal jugular vein and receives lymph from a wide area which includes the anterior floor of mouth, oropharynx and larynx. It is important to realize that contralateral

TABLE 18.1 Neck levels as defined by the American Academy of Otolaryngology-Head and Neck Surgery[6]

Level	Clinical location	Surgical boundaries	Radiological boundaries
Ia	Submental triangle	S: Symphysis of mandible I: Hyoid bone A (M): Left anterior belly of digastric P (L): Right anterior belly of digastric	Nodes above the level of lower body of hyoid bone, below mylohyoid muscles and anterior to a transverse line drawn through the posterior edge of submandibular gland on an axial image
Ib	Submandibular triangle	S: Body of mandible I: Posterior belly of digastric A (M): Anterior belly of digastric P (L): Stylohyoid muscle	
IIa	Upper jugular	S: Lower level of bony margin of jugular fossa I: Level of lower body of hyoid bone A (M): Stylohyoid muscle P (L): Vertical plane defined by accessory nerve	Superior and inferior limits as described under surgical boundaries Nodes posterior to a transverse plane defined by the posterior surface of submandibular gland and anterior to a transverse line drawn along the posterior border of the sternomastoid. NOTE: Nodes lying medial to the carotids are retropharyngeal and not level II
IIb	Upper jugular	S: Lower level of bony margin of jugular fossa I: Level of lower body of hyoid bone A (M): Vertical plane defined by accessory nerve P (L): Posterior border of SCM	
III	Mid Jugular	S: Level of lower body of hyoid bone I: Horizontal plane along inferior border of anterior cricoid arch A (M): Lateral border of sternohyoid muscle P (L): Posterior border of SCM or sensory branches of the cervical plexus.	Superior and inferior limits as described under surgical boundaries Nodes anterior to a transverse line drawn on each axial scan through the posterior edge of the SCM and lateral to the medial margin of the common carotid arteries
IV	Lower jugular	S: Horizontal plane along inferior border of anterior cricoid arch I: Clavicle A (M): Lateral border of sternohyoid muscle P (L): Posterior border of SCM or sensory branches of the cervical plexus.	Superior and inferior limits as described under surgical boundaries Nodes anterior to a transverse line drawn on each axial scan through the posterior edge of the SCM and lateral to the medial margin of the common carotid arteries
Va	Posterior triangle	S: Convergence of SCM and trapezius muscles I: Horizontal plane along inferior border of anterior cricoid arch A (M): Posterior border of SCM or sensory branches of the cervical plexus P (L): Anterior border of trapezius muscle	
Vb	Posterior triangle (supraclavicular)	S: Horizontal plane along inferior border of anterior cricoid arch I: Clavicle A (M): Posterior border of SCM or sensory branches of the cervical plexus. P (L): Anterior border of trapezius muscle	Nodes posterior to a transverse line drawn on each axial scan through the posterior edge of the SCM
VI	Anterior compartment	S: Hyoid bone I: Sternal notch A (M): Common carotid artery P (L): Common carotid artery	
VII	Superior mediastinum	S: Sternal notch I: Innominate artery A (M): Common carotid artery P (L): Common carotid artery	

S = superior; I = inferior; A = anterior; P = posterior; L = lateral; M = medial; SCM = sternocleidomastoid.

TABLE 18.2 Classification of neck dissection techniques

Radical neck dissection (RND)	Removal of levels I–V, accessory nerve, internal jugular vein and SCM
Modified radical neck dissection (MRND)	Removal of levels I–V dissected; preservation of one or more of the accessory nerve, internal jugular vein or SCM (types I, II, III respectively)
Selective neck dissection (SND)	Preservation of one or more levels of lymph nodes.
Extended radical neck dissection (ERND)	Removal of one or more additional lymphatic and/or non-lymphatic structures(s) relative to a radical neck dissection, e.g. level VII, retropharyngeal lymph nodes, hypoglossal nerve

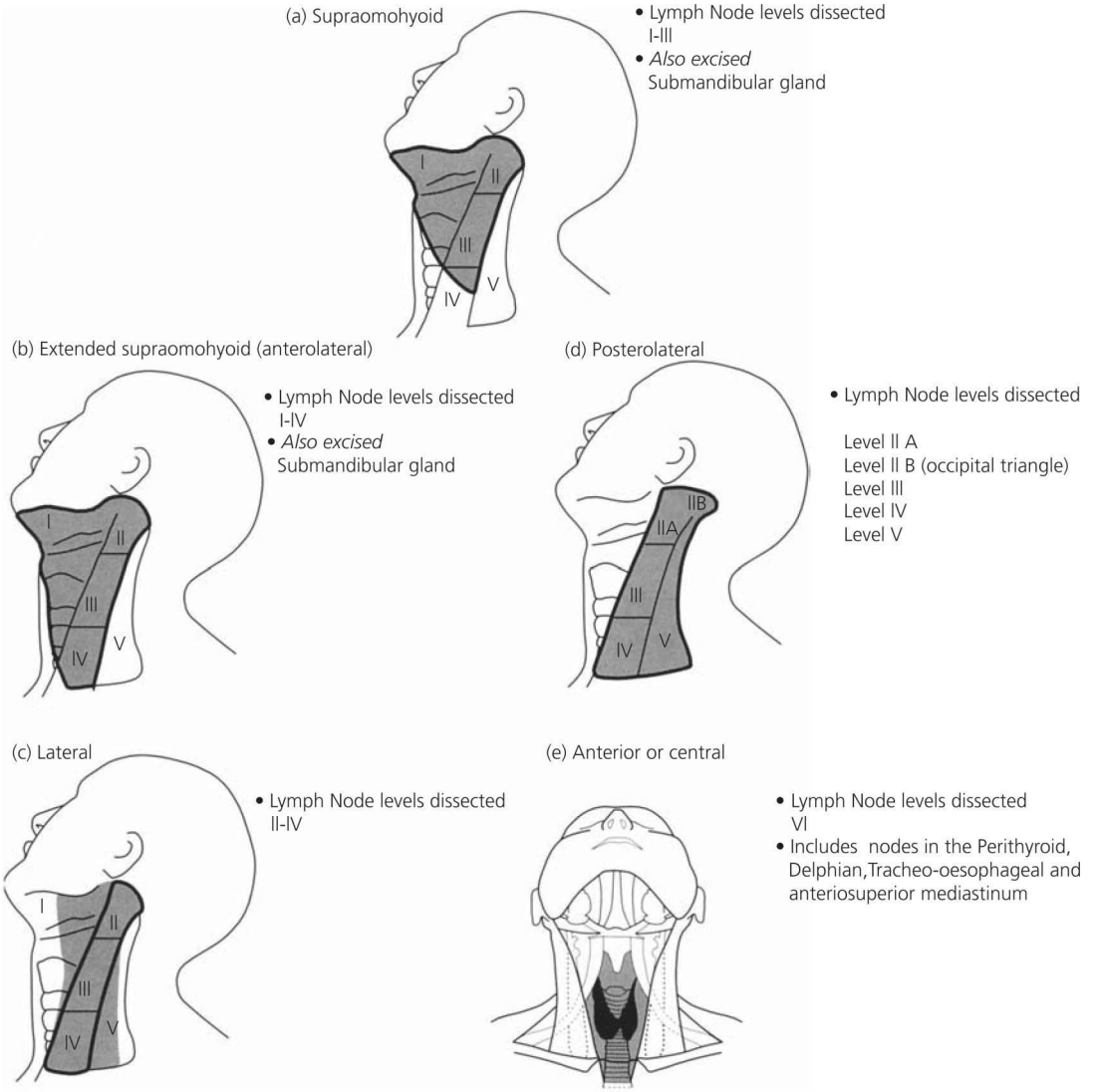

Figure 18.2 Types of selective neck dissection **(a)** Levels I-III (supraomohyoid); **(b)** levels I-IV (extended supraomohyoid; **(c)** levels III-IV (lateral); **(d)** levels III-IV (posterolateral); **(e)** level VI-VII (anterior/paratracheal).

neck spread may occur early in those tumours situated in or near the midline.

- The nasopharynx, nasal cavities and sinuses drain via the junctional nodes into the upper deep cervical nodes (levels II and III) having passed through retropharyngeal or submandibular lymph nodes.
- The oropharynx similarly drains into the upper, middle and lower deep cervical nodes (levels II, III and IV) again either directly or via the retropharyngeal nodes. Within these areas of deep lymph node collections in the neck, certain nodes can reach quite large proportions.
- The oral cavity has a wide area of drainage and this is important because there is often free communication between the two sides of the tongue. The posterior parts of the oral cavity either drain directly into the upper deep cervical nodes (level II/III) or indirectly via the submandibular nodes (level Ib). More anterior parts of the oral cavity and tongue also drain to these nodes but, in addition, may drain to the submental nodes (level Ia) or directly to the jugular nodal chain (levels II to IV). The tongue especially is known to cause 'skip metastases' to level IV.
- The larynx drainage is separated into upper and lower systems based on their embryological origins, with a division that occurs at the level of the true vocal cord. The supraglottis drains through vessels which accompany the superior laryngeal pedicle via the thyroid membrane to reach the upper deep cervical nodes (levels II/III), with a greater tendency for bilateral nodal drainage. The lower system drains directly into the deep cervical nodes (levels III/IV) through lymphatics which pass through or behind the cricothyroid membrane and also into the prelaryngeal, pretracheal or paratracheal nodes (level VI) before reaching the deep cervical nodes. Because the vocal cords are relatively avascular, they have an extremely sparse lymphatic drainage and, as such, lymph node metastases from small carcinomas at this site are uncommon.

- The hypopharynx is similar to the supraglottic larynx, and both may have contralateral spread, particularly in those areas that are either close to the midline or have significant communications across the midline such as the epiglottis, posterior pharyngeal wall and post-cricoid region. Drainage is to levels III, IV, VI and VII.

The region-specific drainage translates well into clinical practice and it is possible to predict the site of a primary tumour based upon the distribution of cervical metastases and vice versa. In a landmark study of 1155 patients with previously untreated HNSCC published by Lindberg in 1972,[6] the topographical distribution of clinically evident cervical metastases was set out. This identified distinct patterns of spread to the neck based on the primary site. Histological proof of this concept was produced in 1990 by Shah[7] in a series of 1119 neck dissections.

It is widely accepted that patterns of subclinical microscopic metastases follow a similar distribution. The high incidence of occult metastases in tumours of the oral cavity, pharynx and the supraglottic larynx forms the basis for SND and removal of the echelon lymph nodes which are the most likely sites of initial metastatic deposits. The echelon nodes for each site are as follows: levels I, II and III for the oral cavity, levels II, III, IV for the oropharynx, larynx and hypopharynx and levels IV, VI and VII for the thyroid gland. For the parotid gland, the first echelon lymph nodes are the pre-auricular, periparotid and intraparotid lymph nodes along with those in level II, III and the upper accessory chain (level Va). For the submandibular and sublingual gland, the echelon lymph nodes lie in levels I, II and III.

METASTATIC BEHAVIOUR IN THE PREVIOUSLY TREATED NECK

Treatment modalities can affect tumour–host equilibrium in unpredictable ways and these include surgery, radiotherapy and chemotherapy.

Surgery can undoubtedly mechanically alter the locoregional tumour environment. Considerable gaps between lymphatics mean that collateral channels form, and the ability to do this relates to the nature of connective tissue through which the lymphatics must grow. These mechanical effects can alter patterns of lymphatic metastatic spread and divert lymph flow to the contralateral neck and sometimes even cause retrograde spread. Surgical scarring can trap tumour cells although this may not always ultimately lead to established local recurrence.[8] It seems sensible to suggest that gentle handling of cancer tissues may decrease the amount of exposure that a surgical wound gets to free cancer cells and as such minimize the potential for any growth.

There is evidence in the literature that the systemic cellular immune response is significantly compromised following locoregional radiation therapy (RT) in head and neck cancer patients.[9] Radiation is associated with changes in the regional lymph nodes and lymphatics in general. Thus, within a few days of starting RT, there is a decrease in the numbers of lymphocytes within lymph nodes and thickening of the walls of both lymph nodes and blood vessels can be noted. Some of these changes explain why previous RT can cause lymphatic obstruction and shunting of lymph both into the subdermal vessels and also to the contralateral neck. All of the above lead to unpredictable changes in the pattern of lymphatic drainage, and thus, the echelon levels described above for the various sites will not be applicable to disease recurrence following treatment.

OCCULT NODAL DISEASE

The term occult disease is used to describe the presence of metastases in the neck nodes that cannot be clinically or radiologically identified. This falls into two categories: occult metastases that can be identified on light microscopy and micrometastases measuring less than 2mm that need special histological techniques (immunohistochemistry, step serial sectioning and molecular analysis) for identification. The incidence of occult disease as assessed by routine histological examination varies by the site and stage of tumour (**Table 18.3**), but use of molecular techniques to look for metastatic disease will increase the incidence rates.

TABLE 18.3 The probability of cervical metastases (N) related to primary (T) staging in patients with HNSCC

Primary site	T-Stage	N0%	N1%	N2–N3%
Floor of mouth	T_1	89	9	2
	T_2	71	18	10
	T_3	56	20	24
	T_4	46	10	43
Oral tongue	T_1	86	10	4
	T_2	70	19	11
	T_3	52	16	31
	T_4	24	10	66
Retromolar trigone Anterior faucial pillar	T_1	88	2	9
	T_2	62	18	20
	T_3	46	21	33
	T_4	32	18	50
Nasopharynx	T_1	8	11	82
	T_2	16	12	72
	T_3	12	9	80
	T_4	17	6	78
Soft palate	T_1	92	0	8
	T_2	64	12	24
	T_3	35	26	39
	T_4	33	11	56
Base of tongue	T_1	30	15	55
	T_2	29	14	56
	T_3	26	23	52
	T_4	16	8	76
Tonsillar fossa	T_1	30	41	30
	T_2	32	14	54
	T_3	30	18	52
	T_4	10	13	76
Supraglottic larynx	T_1	61	10	29
	T_2	58	16	26
	T_3	36	25	40
	T_4	41	18	41
Hypopharynx	T_1	37	21	42
	T_2	30	20	49
	T_3	21	26	54
	T_4	26	15	58

The natural history and the clinical significance of occult metastases is an important, yet largely unanswered question. Neck dissection may arrest progress of some cancer cells. However, a lymph node may be negative on examination because either cancer never reached it or if it did, it was not retained or indeed was destroyed. This has led to several controversies in the management of the occult neck. It is important to address this question because this affects whether or not the disease needs to be treated and by what method. Observational data suggests that the conversion rate from the N0 to the N+ neck without neck treatment is similar to the incidence of pathological positive nodes in END specimens (around 30%).[8] There is no doubt that occult neck disease does have the potential to manifest itself, but it is impossible to predict with reasonable certainty in individual patients. This is one of several arguments that justify the elective treatment of the occult neck. The clinical significance is discussed in depth in 'The N0 neck' below.

MICROMETASTASES

Micrometastases are deposits of cancer cells less than 2 mm in size.[10] Presence of micrometastases upstages the neck status. One of the many goals of translational research in cancer has been to refine disease prediction by detecting tumour-specific molecular alterations in histological normal tissues either at resection margins or identifying 'sub-pathological' metastases in regional lymph nodes. Specific clonal genetic changes seen in tumour cells can be used as molecular markers for their detection in lymph nodes. However, the heterogeneity seen in HNSCC, like other solid cancers, precludes the use of a single tumour specific marker. Thus, these studies are dependent on the amplification of less specific epithelial genes or a panel of their transcripts.

Several molecular markers have been used to identify the presence of 'sub-pathological' metastases in lymph nodes. Using immunohistochemistry, micrometastases can be detected in between 5% and 25% of tumour-positive ENDs of clinically N0 necks,[11, 12] with upstaging occurring in up to 12% of patients.[13, 14] Using techniques such as quantitative reverse transcriptase-polymerase chain reaction (QRT-PCR) results can be obtained within two hours of tissue harvesting. An isolated tumour cell is a further category of micrometastases; equating to single cells or clusters of cells no more than 0.2 mm in size. Where identified, they are still classified as N0. However, isolated tumour cells are classified as N1 in cutaneous malignant melanoma and Merkel cell carcinoma.[15]

The clinical significance of micrometastases is undetermined. Prospective studies have used different markers and techniques to assess micrometastases and have arrived at diametrically opposite conclusions. In the absence of a universally acceptable marker or a battery of markers, it will be difficult to design clinical trials. Because of the unknown prognostic significance of micrometastases or indeed implications for additional post-operative treatment, the extra work involved in discovering it on a routine basis is not currently justified.

CYSTIC NECK METASTASES

Cystic neck metastases are usually of oropharyngeal origin, with the most common sites being the tonsil or tongue base. Human papilloma virus (HPV) related tumours are more often associated with cystic metastases than HPV negative tumours.[16] These lymph node metastases tend to have a better prognosis than their non-cystic counterparts. This has been reported as branchiogenic carcinoma in the past. Any diagnosis of branchiogenic carcinomas should be viewed with scepticism.[17, 18] The majority of branchiogenic carcinomas are in fact cystic metastases from oropharyngeal carcinoma and not true carcinomas arising in a branchial cleft cyst. Given the exponential rise in HPV positive oropharyngeal carcinoma throughout the world, any cystic level II neck mass in an adult should be considered as a potential metastasis and should be investigated as recommended in Chapter 17, Neck metastases from an unknown primary, that deals with the investigation and management of carcinoma from an unknown primary.

PROGNOSTIC NODAL FEATURES

There are a number of features of metastatic cervical nodal disease which indicate a poor prognosis (**Box 18.1**). However, much of the data used to arrive at these conclusions is retrospective and readers should consider whether primary surgical or non-surgical treatments were used in the descriptive observational case series. Surgery accurately stages disease and primary radiotherapy will not upstage occult neck disease or define extranodal extension (ENE), previously known as extracapsular spread. Lefebvre et al[19] looked at the impact of various regional factors on regional recurrence and distant metastases. This study with 1330 patients showed that irrespective of T staging, ENE, three or more positive nodes and positive level IV nodes doubled the risk of regional recurrence and trebled the risk of distant metastases. In the era of HPV-induced oropharyngeal SCC (OPSCC), there is emerging evidence that the number of involved nodes may have greater prognostic significance than ENE.[20] Matted nodes identified on pre-treatment imaging, defined as three nodes abutting one another with loss of an intervening fat plane replaced by ENE, is another factor that may confer a worse prognosis for patients with HPV OPSCC undergoing CRT.[21]

Extranodal extension

ENE occurs when the cancer has penetrated and infiltrated beyond the lymph node capsule. There is a consensus that the presence of ENE in a lymph node is associated with a poor prognosis.[8, 22–26] Both prospective and retrospective evidence

BOX 18.1 Prognostic nodal features

- Site, size and number
- Low neck nodes
- Extracapsular spread / Matted nodes
- Morphology
- Bilateral and contralateral spread (N2c disease)

suggests that ENE decreases survival rates by approximately half compared to those patients whose tumour was confined to the nodes. Also, patients who have occult involvement of nodes but ENE statistically do worse.[8, 27] A recent meta-analysis concluded that perinodal spread adversely affected 5-year survival, with a summarized odds ratio of 2.7.[28] Some workers have noted that invasion of the soft tissues of the neck by tumour lowers treatment success rates by 80%. Other studies show that patients with ENE are at increased risk of local recurrence, distant metastases and that the time to recurrence is shorter. Indeed, it has been suggested that stratification of disease by the presence or absence of ENE would offer a more accurate prognosis than the current TNM system.[29] It is likely that ENE may have a differential impact depending on the primary sites. For instance, Oosterkamp et al[30] showed that ENE adversely affected survival in laryngeal cancer by increasing the risk of metastases nine times, compared to a three times greater risk in patients without this finding.

Currently, it is not clear whether or not ENE represents increase in tumour burden or an increase in tumour aggressiveness. Toker[31] demonstrated that a primary rest of tumour emboli within the node capsule may lead to ENE occurring quite early in the metastatic process and as such may represent an anatomical variation rather than an aggressive tumour. In addition, not all nodes within a neck dissection specimen show ENE and there may be a threshold volume of ENE above which the prognosis is poor.

The literature almost universally recommends that the standard treatment if ENE is detected following surgery is to add post-operative radiotherapy or chemoradiation, even for those who have only one node involved.[8, 32, 33] In the presence of ENE, there is level 1 evidence in support of concomitant cisplatin with post-operative radiotherapy for patients fit enough to receive this.[33] However, there are some questions raised over how this evidence relates to the particular population of patients with HPV related OPSCC, following primary surgical management. This is discussed below.

Retropharyngeal nodes

Tumours that are associated with these nodes include primary disease of the oropharynx, paranasal sinuses and pyriform sinus as well as advanced primary tumours at any site together with massive unilateral or bilateral neck disease, which presumably involves retropharyngeal nodes due to shunting from obstructed lymphatic ducts or channels. Retropharyngeal node invasion is almost always a radiological diagnosis (**Figure 18.3**). There are a number of reports in the head and neck literature that associate the presence of retropharyngeal nodes with a very poor prognosis,[8, 34, 35] but a study of 51 patients concluded otherwise.[36]

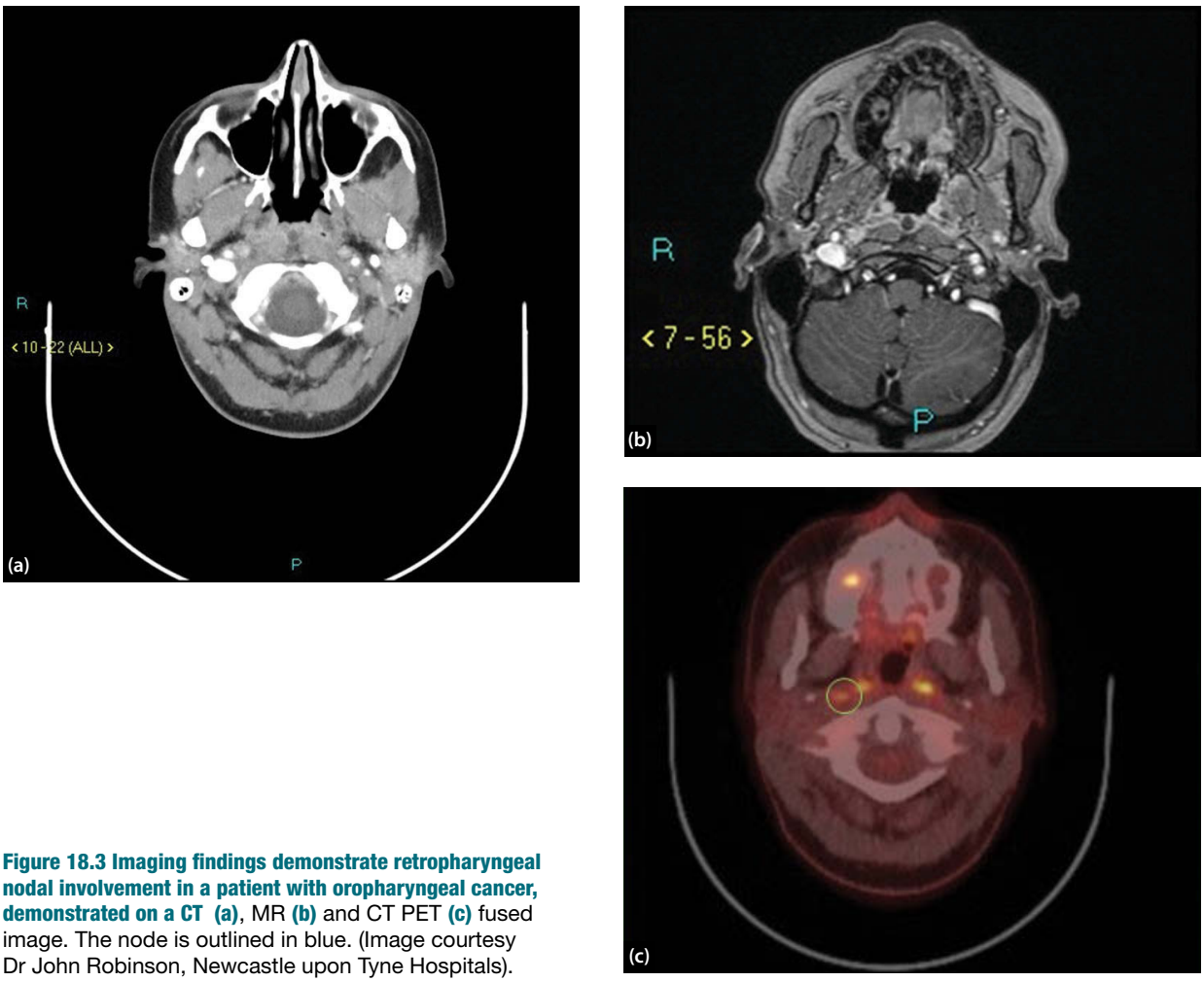

Figure 18.3 Imaging findings demonstrate retropharyngeal nodal involvement in a patient with oropharyngeal cancer, demonstrated on a CT (a), MR **(b)** and CT PET **(c)** fused image. The node is outlined in blue. (Image courtesy Dr John Robinson, Newcastle upon Tyne Hospitals).

CLINICAL STAGING

A classification system is essential for documentation of disease extent, comparisons of results between centres and stratifying patients for inclusion into trials. This is based not only on the presence or absence of cervical lymphadenopathy but also the size, number and laterality of the lymph nodes. The joint UICC and AJCC classifications for regional cervical lymphadenopathy have had substantial changes made to them, in the latest 8th edition (**Tables 18.4–18.6** and **Figures 18.4** and **18.5**). They now take into account ENE status

TABLE 18.4 Clinical N staging for cervical metastases[5, 15]

N category	Criteria
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node, 3 cm or smaller in greatest dimension and ENE-negative
N2a	Metastasis in a single ipsilateral lymph node larger than 3 cm but not larger than 6 cm in greatest dimension and ENE-negative
N2b	Metastasis in multiple ipsilateral lymph nodes, none larger than 6 cm in greatest dimension and ENE-negative
N2c	Metastasis in bilateral or contralateral lymph nodes, none larger than 6 cm in greatest dimension and ENE-negative
N3a	Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE-negative
N3b	Metastasis in any node(s) and clinically overt ENE-positive

ENE = Extranodal Extension. Defined as: The presence of skin involvement or soft tissue invasion with deep fixation/tethering to underlying muscle or adjacent structures or clinical signs of nerve involvement is classified as clinical extra nodal extension.

TABLE 18.5 Clinical N stage for Human Papillomavirus (p16) positive associated oropharyngeal carcinoma[5, 15]

N category	Criteria
NX	Regional nodal status cannot be assessed
N0	No regional lymph node metastases
N1	One or more ipsilateral lymph nodes, none larger than 6 cm
N2	Contralateral or bilateral lymph nodes, none larger than 6 cm
N3	Lymph node(s) larger than 6 cm

TABLE 18.6 Pathological N stage for Human Papilloma virus associated oropharyngeal carcinoma[5, 15]

P category	Criteria
NX	Regional nodal status cannot be assessed
N0	No regional lymph node metastases
N1	Metastasis in 4 or fewer lymph nodes
N2	Metastasis in more than 4 lymph nodes

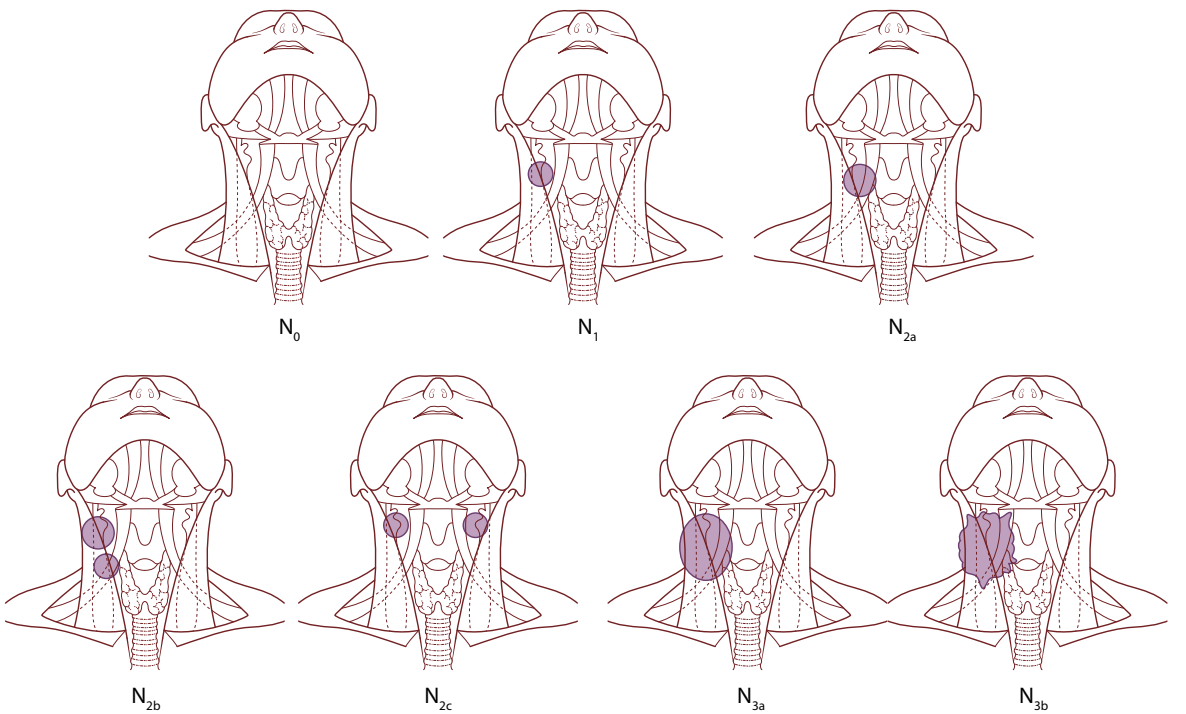

Figure 18.4 Clinical N staging for non-human papillomavirus associated oropharyngeal carcinoma.

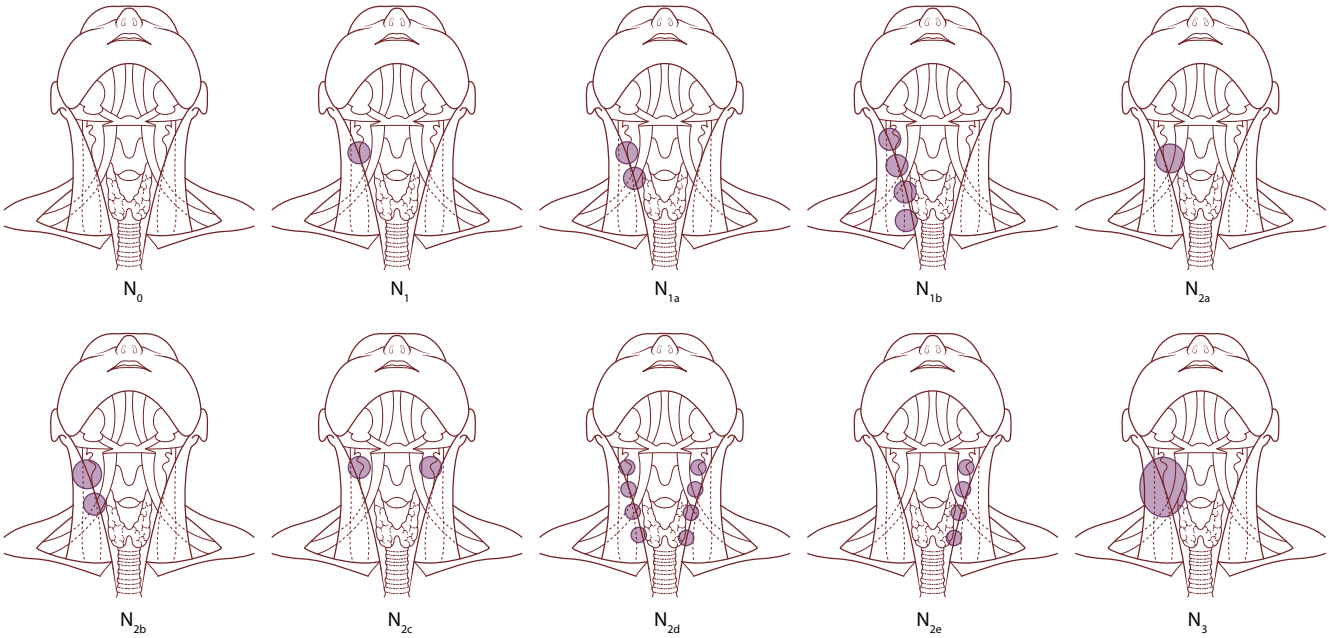

Figure 18.5 Clinical N staging for human papillomavirus associated oropharyngeal carcinoma.

and HPV (P16) status, and split the staging into distinct clinical and pathological classification. This is covered in detail within Chapter 4, Staging of head and neck cancer.

A retrospective analysis of 1190 patients between 1985 and 2007 demonstrated that the inclusion of ENE status in addition to the N-stage offered more accurate survival prognosis than the previous TNM staging system.[29] The 8th edition of the TNM staging recognizes a clinical staging group for ENE in p16 negative SCC, called N3b, diagnosed unambiguously on clinical examination alone (e.g. invasion of skin, infiltration of musculature/dense tethering to adjacent structures, or dysfunction of a cranial nerve, the brachial plexus, the sympathetic trunk, or the phrenic nerve) and supported by radiological evidence (**Figure 18.4**). This represents far more advanced disease than many patterns of ENE identified in neck dissection specimens.

The International Collaboration on Oropharyngeal cancer and Network for Staging (ICON-S) has developed[37] and validated[38] a model for HPV related OPSCC, with neck disease resembling the N-staging for nasopharyngeal carcinoma, but without the lower neck disease variable. This work has shaped the 8th edition of the TNM staging systems. There was recognition that 5-year overall survival was similar for N1, N2a and N2b subgroups, the rationale for these stages being grouped together as N1 disease (**Figure 18.5**). The separate TNM staging system for p16 positive cancers is due to the more favourable prognosis of HPV OPSCC, with previously defined advanced disease now being more appropriately classified to fit with the prognostic evidence. There is an anticipated psychological benefit for these patients, in which many previously stage IV tumours will now be stage I.[39]

CLINICAL PRESENTATION OF NECK DISEASE

The pattern of spread of malignant disease to the neck depends upon both patient and tumour factors. These are identified in **Box 18.2**. The site of the primary tumour is important with some sites having a higher incidence of metastases, both palpable and otherwise, at presentation (**Table 18.3**). Neck metastases usually present as neck masses, usually firm to hard on palpation. They may be mobile or fixed to surrounding structures, usually determined by the degree of ENE.

ASSESSMENT OF CERVICAL LYMPHADENOPATHY

Any patient with a head and neck primary tumour requires careful assessment of the neck. This begins with a full clinical examination which may be supplemented by an examination under anaesthetic. Further assessment of the neck with fine needle aspiration / core biopsy cytology and radiological imaging can help confirm or refute the diagnosis. Occasionally, an open biopsy may be required.

BOX 18.2 Factors implicated in pattern of metastatic nodal disease

- Tumour site
- Tumour size
- Tumour thickness
- Previous treatment
- Tumour recurrence

Clinical examination

Clinical examination remains an important initial method of assessing regional lymph nodes and is covered in more detail in Chapter 36, Clinical examination of the neck. Clinical examination of the neck has a variable diagnostic accuracy.[40, 41] Based on a systematic review,[42] physical examination has a sensitivity of 74%, specificity of 81% and an overall accuracy of 77%. This can be particularly difficult in necks that are difficult to examine i.e. following radiotherapy, previous surgery or in short, stocky necks. Nodes in these instances may go unnoticed until they reach a considerable size. In addition, some regions are inaccessible such as the retropharyngeal area.

Fine needle aspiration cytology

In the presence of palpable disease and a proven primary, treatment will usually be directed towards the assessment of the neck disease rather than confirming that a metastasis is present by fine-needle aspiration cytology (FNAC). Few surgeons would ignore a clinically palpable node in the presence of proven primary disease even if the FNAC shows no evidence of malignancy. The technique is particularly useful in the assessment of a palpable node when searching for an unknown primary as the cytological aspirate (which may require a core biopsy according to institutional practice) can be subjected to tests that may help in the search for the primary tumour. For example, evidence of HPV or Epstein–Barr virus transcripts (or their surrogate markers) will point to a primary site in the oropharynx or nasopharynx respectively. The possibility of anaplastic carcinoma or lymphoma usually makes a core-biopsy or open biopsy mandatory. The FNAC technique is easy to perform, can be reported immediately (particularly if a cytopathologist is present in the outpatient clinic) and has overall accuracy rates exceeding 90%.[43] There is, however, a well-recognized learning curve associated with the technique.

Ultrasound scan

This technique can detect the presence of malignant cervical lymph nodes with sensitivity rates between 70% and 90%. When combined with FNAC, this figure increases to 90%. However, the technique requires an expert ultrasonographer to be present in the outpatient clinic, is operator dependent and labour intensive. The addition of power Doppler to assess vascular flow[44] and molecular analysis of the aspirate[45] does improve on these figures. It should be noted that there are no absolute criteria for differentiating benign from malignant disease, but absent hilar echoes and increases in short axis length are generally considered to be features of metastatic neck nodes. Sonoelastography is a new imaging technique where low-amplitude, low-frequency shear waves are propagated through internal organs, while real-time Doppler techniques are used to image the resulting vibration pattern.

The decrease in vibration amplitude caused by the presence of inhomogeneity, such as a tumour within a region of soft tissue, is measured. This has shown promise in the evaluation of neck nodes.[46] There is also an increasing vogue for adding ultrasound with or without guided FNAC to follow up neck disease in patients after chemoradiation.[47]

CT

The diagnostic accuracy of CT scanning in detecting malignant cervical lymphadenopathy is higher than clinical examination. The range of non-malignant cervical lymphadenopathy is 3 mm up to 3 cm, but most authors recognize that nodes greater than 1 cm in size on CT may contain metastatic disease. The criteria used for categorizing metastatic deposits include lymph nodes with short axis diameter larger than 1 cm, cluster of three or more borderline enlarged nodes larger than 0.8 cm, and nodal necrosis or patchy enhancement within the nodes.[48–50]

A meta-analysis of CT vs physical examination with 647 neck dissections showed CT to have a sensitivity of 83% with a specificity and overall accuracy of 83%.[42] This figure has remained stable in a more recent meta-analysis.[51] The detection of malignant disease is based on the fact that as cancer invades the lymph node, its size, shape and characteristics change so that as it enlarges, its centre dies and appears necrotic and there is a thin rim of inflammation around the edge which shows up on scanning as rim enhancement.

It is important to realize that the two most difficult areas in imaging head and neck cancer are the detection of low-volume neck disease and residual and recurrent disease following surgery and irradiation. Based on the above imaging criteria, it is possible to miss a metastatic deposit in an 8 mm cervical lymph node, at which stage, the lymph node would contain 10^8 malignant cells. With increasing use of organ preservation modalities, conventional imaging (CT and MRI) and nuclear medicine imaging have assumed an important role in the assessment of treatment response after chemoradiation.

However, it is important not to rely on imaging alone and management decisions must be made after correlating the clinical findings. Indications for neck imaging are set out in **Box 18.3**.

MRI

This technique can detect cervical lymphadenopathy with overall similar accuracy rates to CT although meta-analyses have found CT to perform better than MRI.[51, 52]

BOX 18.3 Indications for anatomical neck imaging

- Primary tumour assessment
- Careful monitoring of N0 necks (Ultrasonography more likely)
- Assess treatment response
- Assess the difficult neck
- Re-staging recurrent tumours

However, MRI may be better in evaluating the N0 neck and in the presence of deep invasion. Similar criteria for malignancy are used in both techniques. Initial experience with ultrasmall paramagnetic iron oxide-enhanced MRI has shown this modality to have superior diagnostic efficacy compared to conventional imaging.[53, 54]

PET with CT

PET using [18F]-2-fluoro-2-desoxy-d-glucose (^{18}FDG) as a radioactive tracer has proven efficacy in the functional imaging of solid tumours. Tumour cells metabolize more glucose compared to normal tissue and the increased uptake of the glucose analogue FDG can be imaged. However, the major drawback of this technique is the limited morphological information, making the exact anatomical localization of an area of increased glucose metabolism difficult. On its own, ^{18}FDG-PET has inferior sensitivity and specificity compared to conventional imaging,[55] but has been shown to have the ability to change the management in up to 15% of patients when used prior to commencing treatment.[56, 57]

Co-registered anatomical and functional imaging techniques using dual modality PET-CT scanners lead to accurate image fusion, thus harvesting the advantages of both techniques. With relevance to metastatic neck disease, PET-CT has been investigated in the following settings: initial staging, radiotherapy planning, and evaluation of response to radiation or chemoradiation.

There are calls for using this modality in routine practice to stage patients prior to treatment planning, as apart from diagnosis, this may have an impact on the treatment; for example, the presence of distant metastases otherwise not detected on conventional scanning may be picked up on PET imaging, leading to a more palliative approach. For this reason in the UK, recent national guidelines have recommended offering patients PET-CT staging for all T4 hypopharynx and nasopharynx disease, and all N3 neck disease.[58] This can help more treatment resources to be directed to those who are more likely to do well following locoregional treatment.[59] High sensitivity (90–95%) and specificity (95–99%) rates have been observed in the pre-treatment setting.[60–62] PET-CT detection rate for nodes less than 1 cm is reported at 71%.[63] Thus, this modality has poor detection rate (0–30%) in the setting of the N0 neck.[64–66]

Currently the widespread role of PET-CT is confined to detecting the occult primary, detecting unknown distant metastases in certain clinical settings, and for assessment of residual and recurrent disease following irradiation. If a primary site is not immediately apparent on clinical examination, all efforts must be taken to identify the primary site. A detailed discussion of the assessment of the unknown primary can be found in Chapter 17, Neck metastases from an unknown primary.

It is worth noting that false positive results with PET-CT are common in the first few weeks after primary chemoradiation treatment and scans should be deferred until at least 10–12 weeks after completion of treatment.[67] The scan has a high sensitivity (100%) and negative predictive value (98–100%)[68, 69] in the evaluation of the post-treatment neck, and these figures are consistent on meta analyses.[70] Based on this finding, its use has been recommended to avoid salvage neck surgery (see below).

Open biopsy

In general, this diagnostic procedure is best avoided as an initial diagnostic modality. However, in situations where FNAC is not available, equivocal or non-diagnostic, or when the results suggest either a lymphoma or an anaplastic carcinoma, it may be necessary. When a primary site cannot be identified through exhaustive investigations and diagnostic cytology cannot be achieved from a suspicious neck node (most commonly a cystic lesion), the open biopsy should be performed as an oncological procedure, namely as a SND. There is no evidence in the literature that an open biopsy alters the prognosis, as long as correct treatment is instigated within 6 weeks.[32] Any incision should be made to facilitate the removal of the scar via a subsequent standard neck dissection incision and previous surgery may mean that vital structures such as the sternomastoid muscle may have to be sacrificed due to scar tissue.

Sentinel node biopsy

The sentinel node biopsy (SNB) is a diagnostic technique used to assess the presence of occult metastatic disease in the N0 neck. The SNB concept is based on the principle that identification of the echelon nodes and assessing them for metastatic spread will provide information regarding the status of the rest of the neck. Using radioactive probes and/or blue dye around the tumour site, the first to third echelon nodes are identified with the help of gamma cameras and peri-operative hand-held probes; these nodes are subsequently harvested and analyzed for tumour deposits. From a pathological point of view, these nodes undergo a much more comprehensive analysis (step-serial sectioning, immunohistochemistry) as missing a small deposit in the node could result in a wrong decision to not treat the neck. The assumption here is that if these echelon nodes are negative for secondary deposits, it is unlikely for the rest of the neck to have metastases, thus avoiding further treatment to the neck.

It has been shown in patients with early-stage malignant melanoma that selective lymphatic dissection performed after confirmation of positive sentinel node(s) is therapeutically equivalent to elective lymphatic dissection. Although the technique is considered standard for melanoma, breast cancer and other and non-head and neck sites, there have been some concerns regarding the technique in the head and neck. The head and neck lymphatic drainage can be variable with skip metastases, collateral channels are often present and the technique potentially involves the violation of oncologic principles. In addition, the technique is operator dependent with a recognized learning curve[71, 72] and there is an inherent risk of facial nerve damage when assessing parotid nodes. Its role would

appear to be mainly in the treatment of disease within the oral cavity and oropharynx. Injection of the tracer around laryngeal tumours may be cumbersome and satisfactory injection all around the tumour is difficult. Despite these concerns, meta-analysis shows very good sensitivity of SNB for this difficult site.[73] When considering the SNB evidence, the sensitivity of the test would seem most valuable, indicating the risk of false negative results which could lead to under treatment of neck disease. A pooled meta-analysis of non-randomized trials demonstrated that SNB had a sensitivity of 93% for oral cavity cancer.[71] The implications of this are discussed in the section on management of N0 disease below.

Pathology

The head and neck pathologist has the final say in the assessment and staging of cervical lymphadenopathy. Following neck dissection, the specimen should be pinned out on a board and orientated as to the levels, or the specimen separated into respective levels before presenting it to the pathologist. It will then be examined to assess the total number of lymph nodes in the specimen, the number that are positive, the levels that are involved along with the presence or absence of ENE, neural, vascular and lymphatic permeation. Standardization of pathological reporting is essential in order to compare data across centres and to facilitate comparative audit and there is currently a standardized reporting form, which has recently been updated by the Royal College of Pathologists. A detailed treatment of the pathological aspects can be found in Chapter 26, Pathology of head and neck malignancies.

DRAWBACKS IN THE LITERATURE WHEN ASSESSING TREATMENT OUTCOME

The majority of papers published in the literature which relate to HNSCC are retrospective, and because of this some of the controversies that existed fifty years ago have yet to be resolved. Retrospective data suffers from several biases. These include variation in treatment protocols caused by factors relating to the patient, the tumour and treating physician. Diagnostic and treatment expertise varies between centres and therapeutic schedules applied in various ways and at various times. Data collection may require perusal of the notes, which are often incomplete and studies that report different end points are not strictly comparable. For example, survival is the usual end-point reported by head and neck surgeons but when studying the efficacy of any type of neck treatment, locoregional control is more important.

When assessing any single or combination treatment with regards to the control of neck disease, it is important that the study meets the requirements set out in **Box 18.4**. Prospective randomized therapeutic trials control for all these variables but unfortunately there is a paucity of surgical trials in the current head and neck literature, although this situation is improving with several recently published trials and many trials registered and recruiting currently.

BOX 18.4 Prerequisites for studies reporting outcomes of treatment for neck disease

- Homogeneity in disease presentation (untreated necks, recurrent disease, etc)
- Method of treatment should be standardized
- The primary site should be controlled
- Nodal status verified by rigorous histological examination where possible
- Standardized assessment of treatment response
- Clear presentation of regional control rates and disease specific survival
- Adequate follow-up period

TREATMENT OF METASTATIC NECK DISEASE

After controlling for patient and tumour factors, the treatment of metastatic neck disease is usually decided by the stage of neck disease as identified by the joint UICC and AJCC classifications for regional cervical lymphadenopathy.[5, 15] The following section discusses treatment of neck disease for each N stage. It is worthwhile identifying the broad areas where there is a lack of high-level evidence and controversy exists (**Box 18.5**). Most of these topics are being actively investigated and the treatment paradigms are evolving.

It is worth reiterating a few important general principles regarding neck spread when discussing the surgical management of metastatic neck disease. 1) In the untreated neck, patterns of spread may be predictable. 2) In the N0 neck, occult disease is usually found within the first echelon lymph node drainage basin. This permits the principle of SND. 3). Previous treatment alters drainage patterns significantly. 4) Patients with palpable neck disease are more likely to have non-palpable spread in other levels.

BOX 18.5 Controversies in the management of metastatic neck disease

- Significance of occult disease in cervical lymph nodes
- Clinical significance of micrometastases
- Treatment of the N0 neck: elective vs therapeutic
- Role of selective neck dissection in N1 disease
- Role of the sentinel node biopsy in N0 disease
- Role of chemoradiation in advanced neck disease
- Role of superselective neck dissection in the irradiated neck
- Role of neoadjuvant chemotherapy in neck disease
- Optimal treatment for suspected or established bilateral neck disease
- Management of the difficult, inoperable or untreatable neck
- Use of salvage surgery and re-irradiation in recurrent neck disease
- Quality of life following single and multimodality treatment for neck disease

The N0 neck

Historically, evaluation and treatment for the N0 neck has been one of the great dilemmas in head and neck surgery and its treatment today is still controversial. The problem that faces the head and neck oncologist is whether or not to treat the neck electively. The rationale for elective treatment to the N0 neck is the finding of high incidence of subclinical disease in elective RND specimens at the following subsites: the oral cavity, pharynx and supraglottic larynx. As shown in **Table 18.3**, the likelihood of there being involved nodes depends not only on the site of the primary disease but also on tumour size and histological differentiation. The controversy extends to when and how the N0 neck should be treated.

There are a number of treatment options for the N0 neck. These include the following:

- elective surgery
- elective radiotherapy
- adopting a policy of 'wait and see'
- elective neck investigation.

ELECTIVE NECK TREATMENT

Proponents of elective neck treatment maintain it prevents some cancer-related deaths because untreated neck disease can shed tumour into the vascular or lymphatic system and produce distant metastases. Unfortunately, only distant metastases which are seeded from developing nodal disease can be prevented by elective neck treatment and since spread can occur by other routes, or at inception of tumour, then quite clearly the argument for elective treatment is weakened. The evidence for elective neck treatment vs observation is discussed.

Oral cavity

Early stage oral cavity SCC is a common tumour for head and neck surgeons to encounter. There is no controversy; primary surgical management is the treatment of choice for the primary tumour.[75] There has always been great interest in the question of END for cT1-2 N0 oral cavity disease. The other common early stage tumour, glottic cancer, is rarely associated with cervical metastases and as such elective neck treatment is not considered. A recent large RCT has provided significant evidence in support of END for early oral cancer, and is the basis for the UK NICE guidelines recommending END or SNB for this disease.[58] In 2015, D'Cruz et al published outcomes for 500 patients in the New England Journal of Medicine.[76] Patients were randomized into END (level I–III with levels IV and V cleared for obvious or frozen section proven disease) or observation of the neck with therapeutic neck dissection (MRND) for regional recurrence. The primary outcome measure of 3-year overall survival was 80% for the END group and 68% for the therapeutic ND group (p = 0.01). Disease-free survival was also significantly different at 3 years: 70% vs 46%. Ultrasound was used to stage the neck disease pre-operatively. Suspicious disease was noted in less than 1%, indeterminate nodal disease in 7–8% and normal nodal structure found in approximately 92%, with similar results in both treatment groups. The rate of occult nodal disease in the END group was 30%. It could be argued that this is a reason for END in itself, but the authors rightly point out the disparity in ultrasound findings and occult disease. Improved pre-operative imaging could have the potential to correctly identify more patients with involved nodes. Nodal relapse in the therapeutic ND group was 45%, markedly higher than the 30% occult nodal rate in the END, and nodal relapse was more advanced and was associated with a higher rate of ENE in the therapeutic ND group. The authors reasonably suggest the benefit of END could be higher for a population of patients who may not be as rigorously followed up as in this trial. Subgroup analysis suggested the benefit of END may not exist for tumours with a depth of 3 mm or lower.

Prior to this major publication the evidence was less clear; four randomized prospective trials that have examined the issue of elective neck treatment are summarized in **Table 18.7**. Three compared surgical clearance of the neck,[77–79] and one elective neck irradiation,[80] with observation. Only one trial[78] favoured elective neck treatment. Careful 5-year follow-up detected no difference in survival between the two groups in the French trial,[77] but in the delayed treatment group, tumour problems or the patient's general condition precluded an operation when nodes were palpable in two patients, one of the objections to adopting a policy of

TABLE 18.7 Randomized controlled studies in management of the N0 neck

Study	Treatment arms	Number of patients	Positive necks	Disease-free survival	Follow-up (years)	Difference
Pointon and Gleave[80]	ENI	100	–	80%	2	NS
	OBS	105	–	65%		
Vandenbrouck et al[77]	END	39	19	NA	5	NS
	OBS	36	19	NA		
Kligerman et al[78]	END	34	7	72%	3	p = 0.04
	OBS	33	13	49%		
Fakih et al[79]	END	30	10	63%	1	NS
	OBS	40	23	52%		
D'Cruz et al[76]	END	245	81	70%	3	p < 0.001
	OBS	255	146	46%		

ENI = Elective neck irradiation; OBS = Observation; END = Elective neck dissection; NA = Not available; NS = Not significant.

'wait and see' for N0 disease. In addition, more than 50% of patients in both arms received radiation, which may have contributed to the lack of difference. Although the trial by Fakih et al[79] showed no difference in control rates between the arms, it must be noted that the results reported were 1-year survival data, despite median follow-up period of 20 months. Careful perusal shows that patients who underwent elective treatment did well in all comparisons, without achieving statistical significance. It must also be noted that all these studies are not adequately powered. Many retrospective studies and recently, other prospective non-randomized studies, including an evidence-based review,[32] that have looked at the treatment of the N0 neck in oral cavity carcinomas,[81–85] suggested improved outcome when the neck was electively treated. A recent large multicentre trial of 415 patients showed the sensitivity was 86%.[86] Patients with early stage T1-2N0 appeared to have no oncological compromise, despite only 94 of the 415 undergoing neck dissection. The evidence base pertaining to both END and SNB were assessed by the National Institute for Health and Care Excellence in 2016. Based on a systematic review and an original health economic model, the NICE guidelines made two explicit recommendations pertaining to the management of N0 disease in T1 and T2 oral cavity cancer:

- surgical management of the neck should be offered to all patients
- sentinel lymph node biopsy should be offered instead of END unless they need cervical access at the same time (for example, free-flap reconstruction).[58]

Other head and neck primary sites

A 'wait and watch' policy will result in 25–35% of patients presenting with overt disease, needing therapeutic neck treatment, although the results from the randomized trials quoted above suggest a much higher conversion rate. Control rates in this scenario approximate 30–50%, leading to around 15% of patients who have progressive disease. This figure is still higher than the widely accepted 5–7% failure rate where the neck is electively treated. In the absence of high-level evidence for a watch and wait policy, the general consensus in the literature is to err on the side of caution and it is prudent to treat the neck when the risk of occult spread is more than 15–20%. This figure is derived from a rather simplistic decision analysis model performed in the 1990s[87] which showed that at a threshold occult metastatic rate of 20%, the morbidity of treatment is offset by its benefit, and is widely accepted. It must be noted that the surgical treatment considered in the model was radical neck dissection (RND). Many surgeons and oncologists would perform elective neck treatment for lesser probability (5–15%) of occult metastases.[88] The Scottish Intercollegiate Guidelines Network and UK National Multidisciplinary Guidelines also espouse elective treatment of the neck in this scenario.[67, 89]

Currently both END and irradiation are viewed as prophylactic treatments. If one recognizes the significance of occult neck disease as a marker of the ability of any individual tumour to metastasize, thereby providing a significant prognostic indicator of eventual distant metastases and the possible need for systemic adjuvant chemotherapy, then only surgery can provide the histological data to give this information.

BOX 18.6 Indications for elective neck treatment

- 15–20% chance of subclinical neck disease
- Vigilant follow-up not possible
- Clinical evaluation of the neck is difficult
- Access to the neck for reconstruction

CHOICE OF TREATMENT MODALITY FOR THE N0 NECK

Although there are no prospective trials, retrospective data from studies with large numbers suggest that END and irradiation are equally effective in controlling subclinical disease.[90] The choice of treatment modality is dictated by numerous factors including physician and patient choices, QOL issues and how the primary site is managed. When the primary tumour is being treated with radiotherapy, then elective treatment should be with radiotherapy to at least the first echelon lymph nodes (or the whole neck) and where midline extension occurs, treatment should be bilateral. If the primary tumour is being treated with interstitial brachytherapy then the neck may be treated electively with either surgery or irradiation. When the primary tumour is treated with surgery, then elective neck surgery should be carried out since it provides further information for clinical staging, lymph nodes in the area are cleared to give access to vessels for reconstructive purposes, local recurrence rates may be reduced and survival enhanced. The appropriate levels to be dissected out in an SND are based on the site of the primary tumour and this is discussed later. **Figure 18.6** summarizes our recommendations for management of the ipsilateral N0 neck.

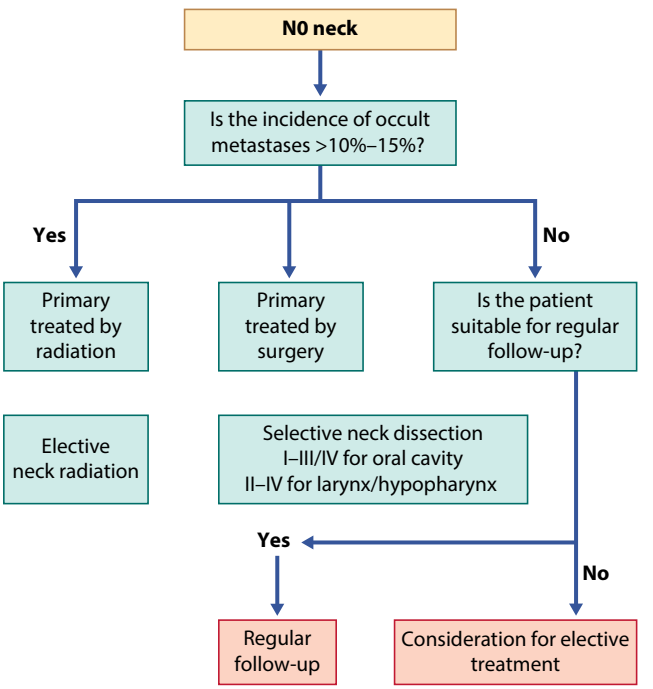

Figure 18.6 Algorithm for management of the N0 neck.

Elective surgery

The pros and cons of elective neck surgery are set out in **Box 18.7** and **Box 18.8** below.

The concept of therapeutic equivalence of SND and comprehensive neck dissection for elective treatment of the neck is widely accepted[91] and based on prospective studies, there is little justification for a comprehensive neck dissection in this setting.[92, 93] Levels II–IV need to be cleared for laryngeal and hypopharyngeal cancer.[93] For patients with oral cavity cancer, SND of at least levels I–III should be carried out, with the addition of level IV for tongue cancers.[92] Levels II–IV are recommended for oropharyngeal cancers.[94] There appears to be little advantage in dissecting level V for any of the mucosal primaries electively.[95–97] Excellent local control rates can be obtained with SND, with recurrence rates around 5% with the primary controlled.

Current work focuses on selecting the levels that need to be dissected in the elective setting. For example, clearance of level IIb during SND involves dissection in a relatively narrow field and significant retraction of the sternomastoid muscle is needed. It is likely that the accessory nerve can be subjected to traction injury and segmental devascularization, causing shoulder dysfunction. Prospective studies[98] have shown that SND causes a small but significant impairment to the shoulder function. The incidence of isolated metastases in this level is very low at 0.3%.[99] Prospective studies have shown little oncological benefit in clearing this level in laryngeal cancer as the occult metastatic rate is low at 0.4%,[99, 100] but higher incidence rates are seen in oral cavity (3.9%) and oropharyngeal (5.2%) cancer. Whether preservation of level IIb necessarily leads to improved shoulder outcomes needs to be verified in prospective studies.

END can undoubtedly serve to pathologically stage the neck, and offer a subsequent indicator of the risk of systemic disease. Local neck and distant metastases are manifestations of the same process and represent the ability of the tumour to metastasize in an individual host.

BOX 18.7 Arguments for elective neck surgery

- The high incidence of occult metastatic disease
- Selective neck dissection has a low morbidity and mortality
- Routine clinical follow-up will not detect the earliest conversion of the neck from N0 to N1 in all patients
- Untreated neck metastases can increase the incidence of distant metastases
- The control rate for neck dissection is decreased if gland enlargement occurs or multiple nodes appear
- Elective neck surgery can be performed during primary surgery
- Anatomical reasons preclude proper neck examination
- Patient compliance for follow-up cannot be assured
- The pathological neck node status from pathology can be used to prognosticate
- The presence of multiple occult metastases will dictate adjuvant irradiation

BOX 18.8 Arguments against elective neck surgery

- Control rates are no lower when a 'wait and see' policy is followed and therapeutic neck dissection is performed
- Careful clinical follow-up combined with imaging has the potential to detect early conversion from N0 to N1
- Radiation is as effective as neck dissection for non-palpable disease
- Elective neck dissection results in a large number of unnecessary surgical procedures associated with inevitable morbidity
- Elective neck dissection removes the barrier to the spread of disease and may have a detrimental immunological effect
- Elective neck dissection can cause a scarred, hypoxic field that can reduce radiation kill.

Elective neck irradiation

Retrospective evidence suggests that external beam radiation of approximately 40–50 Gy to the clinically N0 neck will control occult metastases in up to 90–95% of cases.[101, 102] In addition to the prospective study identified,[80] other retrospective studies evaluating its role in the treatment of patients with SCC of the oral cavity and tongue[103] did show that elective neck irradiation improves locoregional control and may prolong survival in some cases. This is based on the observed rate of conversion of N0 to N+ necks after elective neck irradiation (3–15%) and the expected rate of appearance of nodes when the neck is observed, based on a 20–40% histological incidence of occult neck disease. However, this assumes that all occult lymph node cancer deposits are clinically significant and evidence from other studies suggests this is not necessarily the case.

Elective neck investigation

Another option in the N0 neck is to consider elective neck investigation. Could a radiological investigation such as CT, MRI or ultrasound demonstrate malignant cervical lymphadenopathy at the subclinical stage and if so, could a treatment plan be adopted based on these scans?

It would seem that many of the arguments levelled against neck dissection could be levelled against elective neck imaging.[104] If false positive results are inevitable in the presence of inflammatory neck nodes and false negatives do occur, then imaging could play no role in the routine evaluation of the N0 neck. Treatment should be based upon the understanding of the natural history in question and currently it is probably cheaper and as effective to offer elective treatment to those high-risk patients who need it and 'wait and see' in the others. This will avoid large numbers of unnecessary CT scans and subsequent inevitable inappropriate surgery. It is perfectly reasonable to adopt a policy of 'wait and see' in low-risk necks, i.e. carcinoma of the glottis or the gingiva, but for those that are high risk, waiting for the neck to develop from N0 to N1 may have a detrimental effect on the patient should not to be recommended in current clinical practice.

One recent study[105] evaluated the outcome of observing the clinically N0 neck in high-risk patients (mainly oral carcinoma) using ultrasound-guided FNAC (US-FNAC) for follow-up after transoral excision. Patients were followed up for between 1 and 4 years using palpation and US-FNAC. The high salvage rate (71%) was attributed to a strict follow-up policy using US-FNAC and concluded that a policy of 'wait and see' was justified. Although the authors did not identify the T staging of the primary tumour, some neck failures might have been prevented by elective treatment rather than elective investigation.[106, 107]

THE CONTRALATERAL N0 NECK

In the setting of a unilateral primary and ipsilateral metastases, traditional data suggest that the contralateral neck has a very high incidence of occult metastases, between 30% and 70%, especially in supraglottic,[108–110] hypopharyngeal[111–114] and oropharyngeal tumours.[94, 115] In the presence of advanced primaries at high risk of occult spread, contralateral neck treatment is warranted. Recurrence in the untreated contralateral neck has been shown to be the commonest cause of failure in supraglottic cancer, with improved local control and 2-year survival when dissected.[116–119] There is no benefit in clearing level IIb in the contralateral N0 neck.[99, 120]

The management of the contralateral cN0 neck has again gained prominence as a discussion point, with the rise in popularity and interest in transoral surgical techniques in managing oropharyngeal carcinoma. This technique particularly lends itself to the common scenario observed in HPV positive OPSCC; small-volume lateralized primary tumours, with ipsilateral nodal disease. With this clinical presentation of disease, the most common treatment modality would be primary chemoradiotherapy. Radical treatment dose would be given to the primary site and ipsilateral neck, with prophylactic dose (commonly 54 Gy) to the contralateral neck. The authors offer transoral robotic surgery for this disease and have routinely performed a contralateral staging SND as part of the surgery. They have observed a lower than expected rate of contralateral occult nodal disease in this population. Only 5 out of 60 patients were found to have occult nodal disease, upstaging them to N2c and altering their adjuvant radiotherapy dosage (currently unpublished data). Adjuvant radiotherapy to the contralateral neck was avoided in 55/60 patients. Three of the five patients had HPV negative disease, and it would appear that the risk of occult contralateral nodal disease is higher in the HPV-negative setting. It must be stressed, that the patients treated in this way had lateralized OPSCC, more than 1 cm lateral to the midline of the tongue base, and were highly selected. Nevertheless, these data would suggest that the traditional risk of contralateral occult disease in OPSCC may not be so relevant to this common clinical pattern of disease. Head and neck clinicians should consider how reduced morbidity of treatment can be achieved by avoiding radical treatment to the contralateral neck. Options could consider a staging SND as described, sentinel lymph node biopsy, or serial monitoring with US.

The N+ neck

Management of the N+ neck is continuously evolving as more and more data are accrued. Traditionally, advanced neck disease has needed a combination of surgery and RT for control of disease. The treatment offered to the neck often depends on the modality used to treat the primary site, as seen in the suggested algorithms for patients undergoing primary chemoradiation (**Figure 18.7**) and primary surgery (**Figure 18.8**).

SINGLE PALPABLE METASTASIS IN THE IPSILATERAL NECK LESS THAN 3 CM IN DIAMETER (N1)

Similar to the N0 neck, the choice of modality is usually dictated by the treatment to the primary site. Where the primary is treated with irradiation, the neck is covered as well in the field. ENE is less common in this stage and since the survival figures are good, conservation neck surgery is feasible. In palpable neck disease, traditional teaching is for all five levels to be dissected to clear occult disease; however, it is rare for level I to be involved in primary sites other than the oral cavity. In most cases, the accessory nerve can be preserved, enabling MRND. Based on assessment of the best available evidence,[32] there is no evidence that RND achieves better survival figures than MRND.

It is widely accepted that single-treatment modality gives good control rates for N1 neck disease,[121] although review of large databases suggest that there may be survival advantage in offering adjuvant RT following surgery even for N1 necks.[122] As approximately 50% of clinically N1 necks are upstaged after pathological assessment, many patients subsequently require post-operative radiation. Single modality usually suffices to control N1 neck disease, with both radiation and surgery having equivalent control rates.

Selective neck dissection in the N1 neck as primary treatment

The role of SND in the N+ neck is controversial. There is no doubt that the morbidity of a neck dissection arises largely from level V dissection and there is a low incidence of nodal involvement at this level unless two or more levels (especially level IV) are involved.[32, 123] There is a clear pathological basis for SND in N1 and N2a disease. The proponents for a 'less than five level' neck dissection for N1 disease argue that the distribution of metastases within first echelon lymph nodes in non-palpable disease can be applied to early palpable disease. However, this sort of surgery requires considerable expertise and is not recommended for the trainee surgeon. With experience, a 'conservative MRND' can be performed for N1–N2b to include the entire levels II–IV, with dissection under sternocleidomastoid (SCM) to pull through a significant volume of level V, and to encompass any level IB nodes superficial to the submandibular gland. Careful preservation of the marginal mandibular nerve, the accessory nerve, and

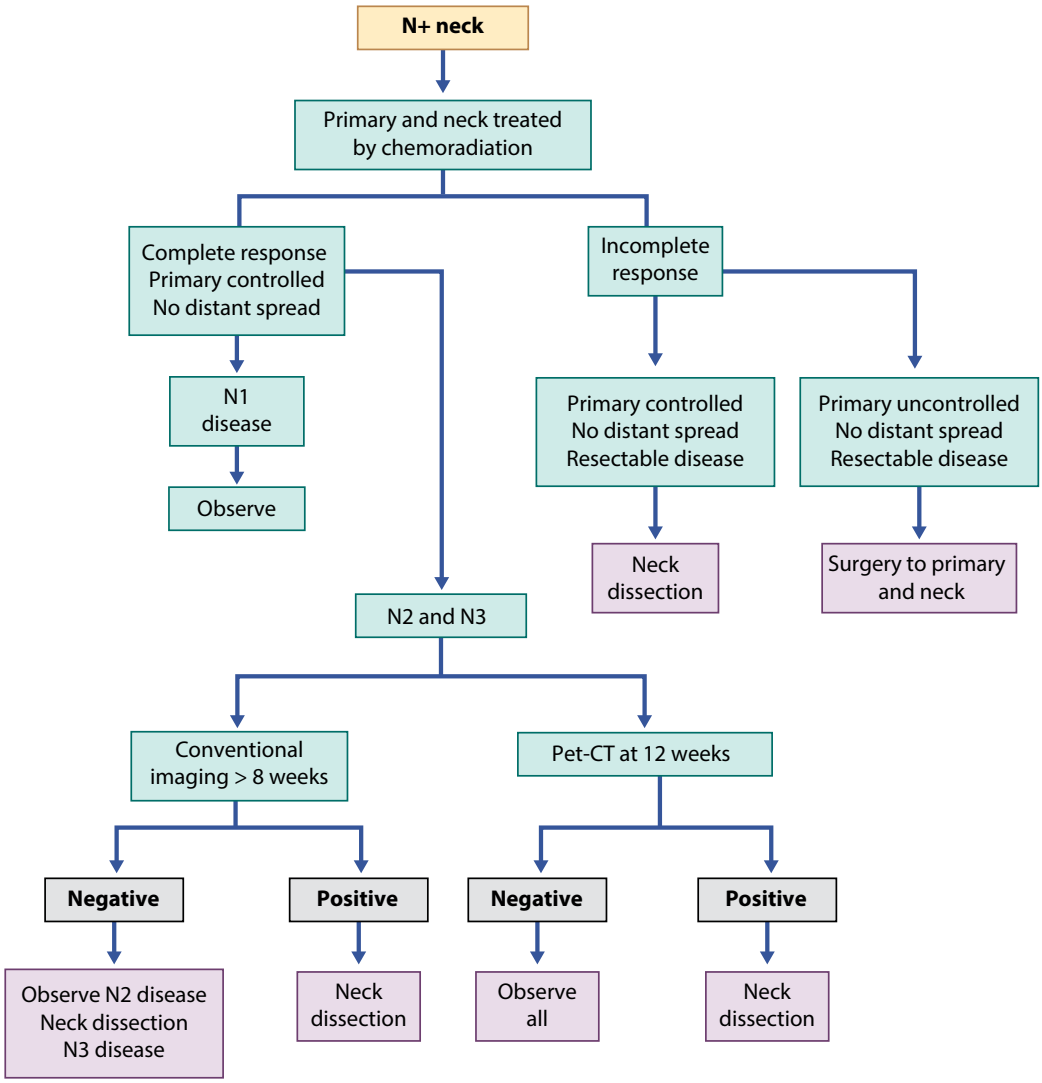

Figure 18.7 Algorithm for management of the N+ neck when chemoradiation is the primary modality.

importantly the small cervical plexus branch that joins to the accessory nerve lateral to the posterior border of the SCM should be performed if considering a conservative approach such as this. Whilst unproven, this sort of conservative approach over a traditional MRND for tumours with predictable nodal metastatic spread may be reasonable, especially if adjuvant therapy can be anticipated to the neck.

Byers et al[124] looked at the outcomes of SNDs in 517 patients. They found that recurrence rates in patients with N1 disease were 5.6% and 35.6% with and without post-operative radiation respectively. Other retrospective studies also vouch for the efficacy of the SND alone in the N1 neck, as long as adjuvant treatment is provided if the disease is upstaged following surgery or other adverse factors exist.[125–130]

Prospective studies are yet to be performed to evaluate this further, but on the basis of a large body of retrospective evidence, it can be concluded that SND may be sufficient treatment for N1 disease confirmed on pathological examination. We recommend that where there is doubt regarding the spread and extent of disease, it is better to perform a comprehensive procedure the first time around.

Concurrent chemoradiation therapy for the N1 neck

Concurrent chemoradiation (given for treating the primary site) offers excellent control rates.[131, 132] No treatment is required in the event of a complete response, but partial responders merit a neck dissection. The type of neck dissection for partial responders is discussed below.

IPSILATERAL LARGE NODE (>3 CM TO 6 CM; N2A) OR MULTIPLE UNILATERAL NODES (N2B)

The treatment depends on the management of the primary and if deemed operable, the neck should be treated with comprehensive neck dissection. If possible, an MRND sparing the accessory nerve gives equivalent control rates to a RND.[32, 133, 134] Larger neck nodes are at a greater risk of ENE, and following primary surgery

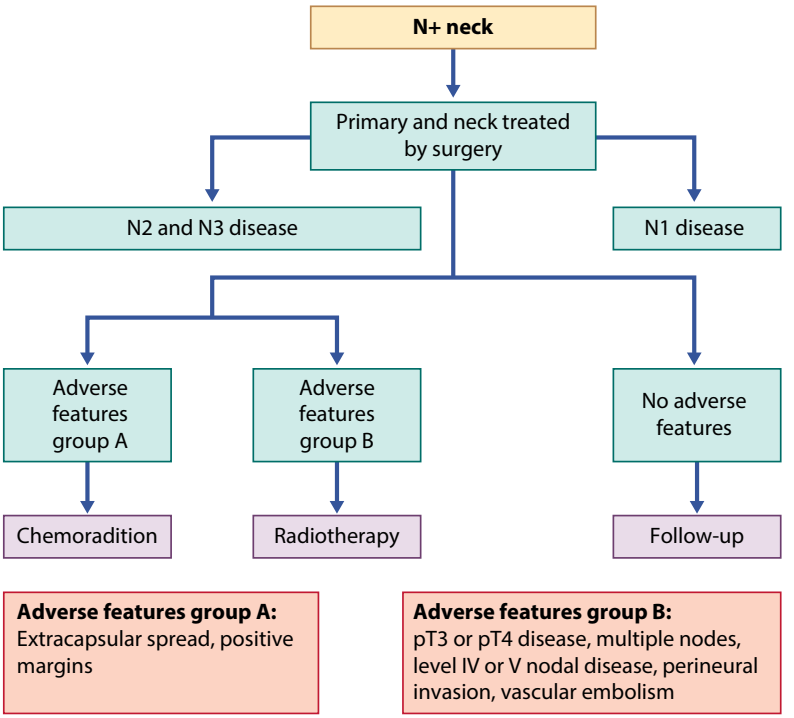

Figure 18.8 Algorithm for management of the N+ neck when surgery is the primary modality.

are best treated by post-operative adjuvant treatment. Analysis of large databases show that adjuvant RT confers a 10% absolute increase in 5-year cancer-specific survival and overall survival for patients with lymph node-positive HNSCC compared with surgery alone.[135] Recent randomized controlled trials performed in Europe and the United States confirm the clear benefit provided by adjuvant chemoradiation in the presence of ENE.[33, 136, 137] If the primary site is being irradiated, and incomplete response ensues, a neck dissection is warranted. Patients who achieve a complete response do not need surgical salvage and the rationale behind this is discussed in more detail in the section on the chemoradiated neck. This group represents advanced disease and retrospective and prospective studies clearly show that if primary surgery is performed, post-operative adjuvant therapy is required to achieve good regional control rates.

BILATERAL AND CONTRALATERAL NODES (N2C)

Patients with bilateral neck nodes are uncommon and occur overall in about 5% of head and neck cancers. As discussed above, N2c disease is more common if the primary sites involved are the tongue base, supraglottic larynx and hypopharynx. Conventionally, the presence of bilateral neck disease was thought to be a grave prognostic sign and this was indicated historically in its staging. However, subsequent careful pathological studies have shown that, in certain instances, this is not so. The prognosis is determined more by the size, number of nodes and by the presence or absence of ENE within the neck rather than by pure laterality. This is particularly true for the supraglottic larynx and in those patients where the bilateral nodes do not feature massive and multiple nodes, treatment can be worthwhile using conventional surgery[138] or chemoradiation. Conservation neck surgery may be possible on the less involved side and post-operative radiotherapy will usually be administered.[1, 139] The decision to treat will often be helped by the location and size of the primary site. Laryngeal tumours with extralaryngeal spread and bilateral nodes are often eminently treatable with laryngectomy and appropriate neck dissection. Patients with bilateral nodes when one side is fixed are usually incurable.

BOX 18.9 Indications for postoperative adjuvant treatment

- Extracapsular spread
- Two or more positive nodes
- N2–3 stages
- Residual disease

MASSIVE NODES (GREATER THAN 6 CM; N3)

The presence of massive nodes is again an uncommon event occurring in patients with head and neck cancer. Only 5% of all patients will present with N3 neck disease in the UK. It is important to realize that many nodes that do reach 6 cm in size are often fixed to the skin and/or underlying structures. The decision whether or not to operate depends upon the stage and site of the primary site, presence or absence of fixation, what the node is fixed to, the experience of the surgeon and the needs of

the patient. The incidence of true fixation of neck masses is often difficult to determine from the literature and varies from series to series with figures from 23%[140] going up to 30%.[141] Fixation to the mandible, sternomastoid muscle or muscles in the midline may not represent as much of a problem as fixation to the brachial plexus or carotid artery. These patients are at high risk of distant metastases and may present a special group where PET-CT scans may be warranted to fully evaluate this problem. Long-term control rates are poor and the benefit of treatment must be carefully weighed against the morbidity caused by it, including the chances of control at the primary site. In many patients, palliation will be the best option. Combined modality therapy leads to better control rates.[142]

THE DIFFICULT NECK

The scenarios that present a difficult neck are set out in **Box 18.10.**

Careful clinical assessment with mandatory radiological imaging will help to assess operability and some of these patients will be helped by extended RND. Fixation to the skull base and brachial plexus is certainly a contraindication to surgical treatment, but fixation to the skin may be treated by wide resection and flap repair.

BOX 18.10 The difficult neck

- Difficult to assess
- Short stocky neck
- Retropharyngeal nodes
- Recurrent disease
- Involvement of vital structures

Carotid invasion: In current day practice, most tumours that present with clinical and radiological signs of carotid invasion are likely to be radiorecurrent.[143] Indications for considering carotid resection include clinical evidence of fixation of the tumour to the carotid, invasion confirmed on imaging, and encroachment of tumour which encompasses more than 270 degrees of the vessel wall. Luminal invasion is rare and pathological evidence of invasion, limited to the adventitia, is seen in only 40–50% of resected arteries.[144–146]

The plan to resect the carotid should always be a pre-operative decision and almost never should a situation arise where this is contemplated for the first time peri-operatively. Pre-operative work up is essential to plan the resection. Balloon occlusion of the artery with single photon emission computer tomography (SPECT) is performed to prognosticate the possibility of neurological deficit following resection. If the test shows adequate cross-flow and does not cause symptoms, there is a lesser need to shunt the artery during resection. If the cross-flow is inadequate, the internal carotid artery should be shunted for the duration of the resection. In all cases, we recommend reconstruction of the artery using an appropriate graft to reduce chances of neurological complications. Most studies report using the saphenous vein graft (**Figure 18.9**). Intra-operative ligation without reconstruction is fraught with a high risk of complications owing to the haemodynamic instability that can occur. This is likely even in those patients who demonstrate good cross-flow and a stump pressure of more than 70 mmHg.

A high-operative morbidity (33% hemiplegia) and mortality (12%) has been quoted from work done in the 1980s, but recent studies where resection and reconstruction of the carotid artery is performed have shown much lower figures.[147, 148] A review of 148 patients published between

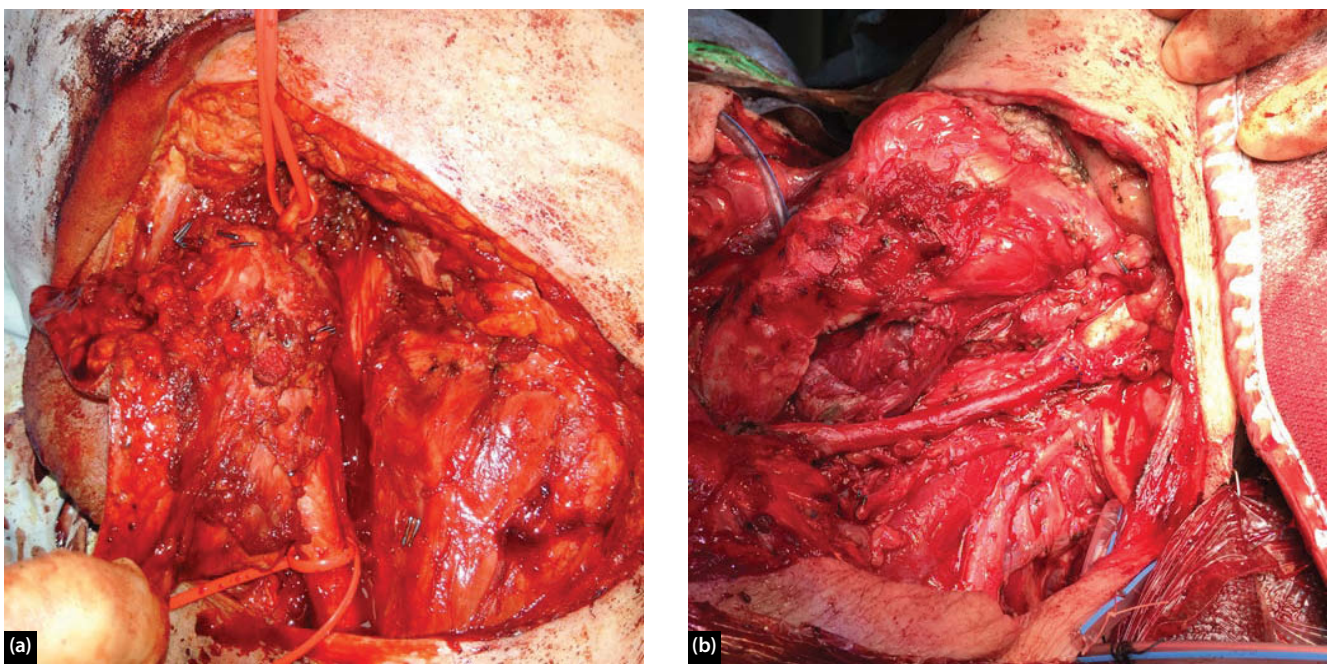

Figure 18.9 (a) A carotid resection in progress. **(b)** The artery has been replaced by a saphenous vein graft.

1987 and 1998 demonstrated combined major neurological morbidity and mortality rates of 10%.[149]

It is well recognized that in untreated patients with HNSCC, the carotid artery may not often be involved even when massive disease is present in the neck and that neck dissection may be possible. However, in the presence of radiological evidence of invasion, surgeons have traditionally opted to resect the carotid. In a review of 90 patients with documented radiological evidence of invasion, Ozer et al[143] showed that this need not be the case and in over 70% of cases dissection of the carotid is feasible and the tumour can be removed without recourse to carotid resection.

Traditionally, carotid resections were regarded to be unrewarding in HNSCC from the point of either achieving locoregional control or improving survival. A review of the literature in 1992[146] reported a 2-year survival rate of 22% following carotid artery resection. This study has been criticised for failing to identify those patients who had been treated previously, for not distinguishing between the treatment of isolated neck recurrence compared with recurrent disease at the primary site as well as the neck. Aggressive disease in a radiated neck may be associated with residual tumour following resection and there is high risk of systemic disease; thus resection of the carotid artery was thought not to affect the natural history of the disease. Papers published in the last decade suggest that poor outcomes are especially seen in patients who have had previous radiation. Those patients with demonstrable carotid invasion who undergo primary surgical resection with or without reconstruction of the carotid may have a much superior outcome, with control rates between 30% and 50% at 5 years.[143, 148–150] There may be a subgroup of patients who present with bulky neck disease and carotid invasion, who are best managed by primary resection and reconstruction with adjuvant radiation.

This is often a difficult scenario and decision should be made after careful consideration of the morbidity and mortality of the procedure, patient expectations and the expertise of the treating team.

THE IRRADIATED N0 NECK WITH RECURRENCE AT THE PRIMARY SITE

Very few studies[151–153] have addressed this question, but they have arrived at the same conclusion. There appears to be no increased risk of occult metastases in this setting and SND is oncologically adequate to clear the neck.

MANAGEMENT OF THE NECK FOLLOWING PRIMARY CHEMORADIATION

Organ preservation protocols have established a firm place in head and neck oncological practice. Using concurrent chemoradiation, they aim to avoid resection and thus sacrifice of the organ where the primary is sited, even for advanced primaries. The following discussion assumes that the primary site has been controlled in all instances.

Although histological evidence of nodal residual disease has been demonstrated in only 40–45% of partial responders, few centres would argue against salvage neck surgery in this setting. The extent of the procedure remains a point of controversy as it is rare to find viable disease in levels that are clinically negative.[154, 155]

Until recently, there had been no universal agreement on how the advanced neck should be dealt with following chemoradiation when a complete response is obtained. Pathological examination of neck dissection specimens has revealed residual disease in up to 25% of patients who have achieved a complete response,[131, 156] but the presence of tumour cells does not indicate that they are viable. Some studies show a clear benefit in regional control when planned neck dissection is undertaken even in the presence of complete response.[131] However, prospective studies of patients with a complete response as assessed radiologically have mature long-term clinical follow-up and show very low regional relapse rates that are comparable to the regional failure rates reported in planned neck dissections series.

Several studies have demonstrated the high sensitivity and negative predictive value of PET-CT imaging to assess residual disease in complete,[68, 157, 158] and partial responders,[68, 69] performed at least 8 weeks after treatment. Earlier scanning increases false positive results and is not recommended. A meta-analysis showed that highest sensitivity results are seen in studies performing PET-CT 10 weeks after treatment.[70] This has been used as a decision-making tool in recommending neck dissection after chemoradiation, with surgery being limited to cases where there is evidence of uptake (**Figure 18.10**). The literature has slowly shifted towards non-surgical management for patients who experience a complete response[159–161] with some international groups endorsing this in consensus statements.[162] Emerging data suggest some role for an SND or even a lesser procedure (superselective neck dissection) in this setting when a complete response is obtained.[163–166]

In 2016, Mehanna et al published the primary outcome results of the PET-NECK trial;[167] 564 patients were randomized to have either an END following CRT, or surveillance of the neck with PET-CT 12 weeks following completion of CRT. Patients were included with N2 or N3 disease at presentation, with primary nasopharyngeal disease excluded from entry to the trial. Patients in the PET-CT surveillance arm underwent ND for residual disease. The trial demonstrated equivalent overall survival between the groups at two years (85% in the surveillance group and 82% in the END group), with fewer neck dissections in the surveillance group (54 vs 221) and a cost saving of approximately £1500 ($2200) per patient undergoing PET-CT surveillance.

The authors make a very important comment following their analysis in suggesting it would be reasonable to monitor residual enlarged neck nodes following CRT, if they are PET-CT negative, in HPV-positive disease. They suggest that in HPV-negative disease, equivocal but enlarged nodal disease on PET CT at 12 weeks should undergo neck dissection (**Figure 18.11**).

In light of this recent level 1 evidence, we recommend that necks staged N2 and N3 undergo PET-CT imaging at 12 weeks (the TNM 8th edition clinical staging[5, 15] does

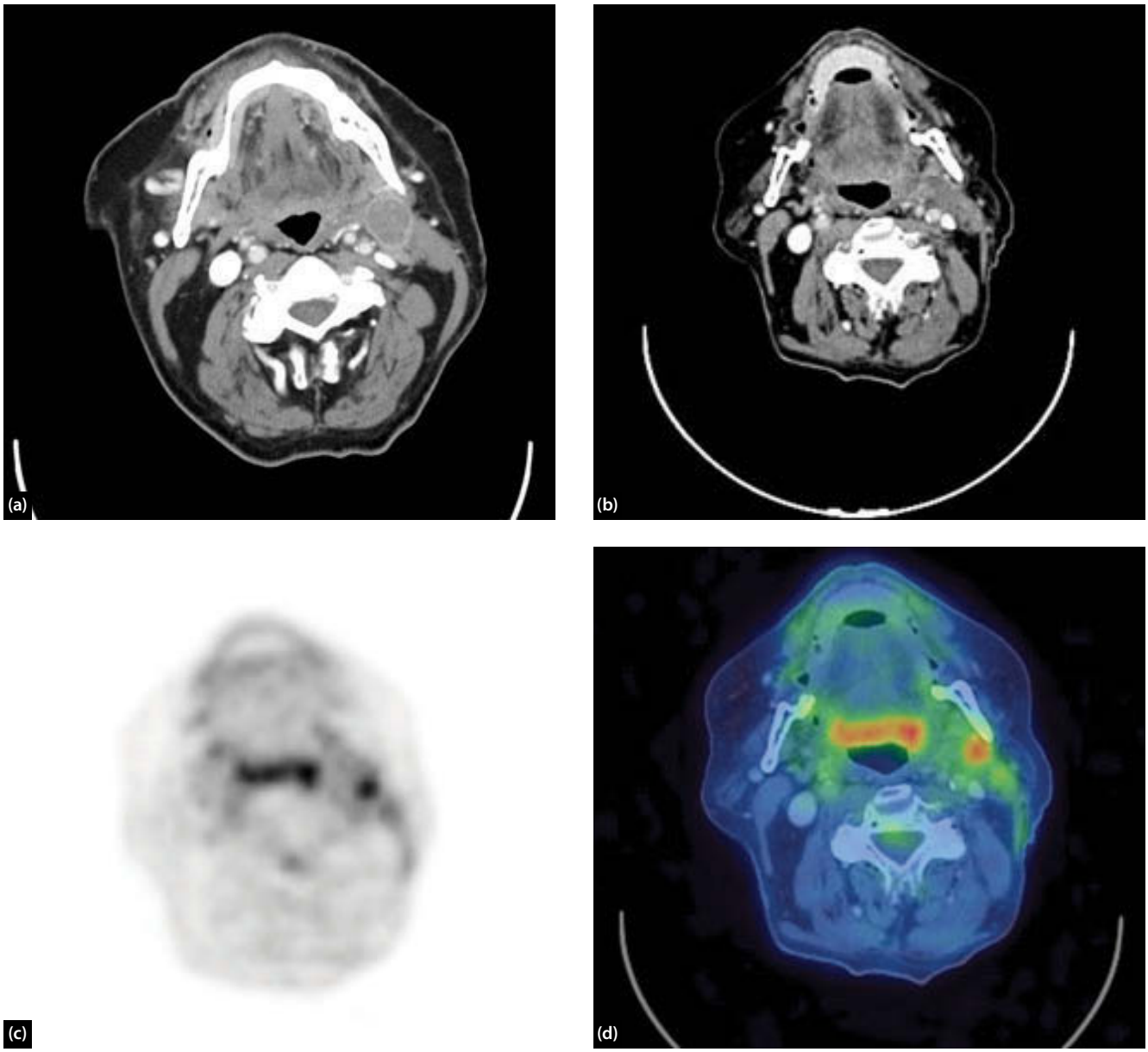

Figure 18.10 **(a)** The pre-treatment CT scan demonstrating a cystic metastasis. Post-treatment CT component of PET-CT scan **(b)** at 14 weeks shows residual nodal swelling that is avid on the PET **(c)** and the fused PET-CT images **(d)**, indicative of residual disease. This patient underwent a neck dissection that confirmed residual disease (Image courtesy Dr Tamir Ali, Newcastle upon Tyne Hospitals.

not allow distinction of a single <3 cm HPV positive node – hence all N1-3 disease should undergo PET-CT imaging at 12 weeks). Complete responders can be observed. Where there is no access to PET-CT, conventional imaging should be performed at 12 weeks. Salvage neck dissection should be considered for residual enlarged nodes.

The PET-NECK trial data has now clarified that complete neck responders can be safely observed.[167] Patients with equivocal PET-CT uptake will be considered partial responders and should be offered neck dissection. Of course, not all of these patients will have pathologically viable tumour. It is the authors' experience that many equivocal neck findings on PET-CT will ultimately turn out to be negative on pathological examination. As discussed above, there has been a move towards SND or even super-SND following CRT, with the recognition that neck morbidity is reduced with less levels dissected. For equivocal responders on PET-CT or more concerning residual findings on PET-CT, what should the extent of neck dissection be? The evidence for this question predates the emergence of PET-CT scanning as a reasonable predicator of response, and comes from series in which many more patients more routinely offered post-CRT neck dissection. However, the series of 177 post-CRT neck dissections described by Robbins et al[166] offers convincing data to support a limited SND in patients with residual disease. Having utilized CT imaging post-CRT, of the 54 patients with pathological residual disease, only two

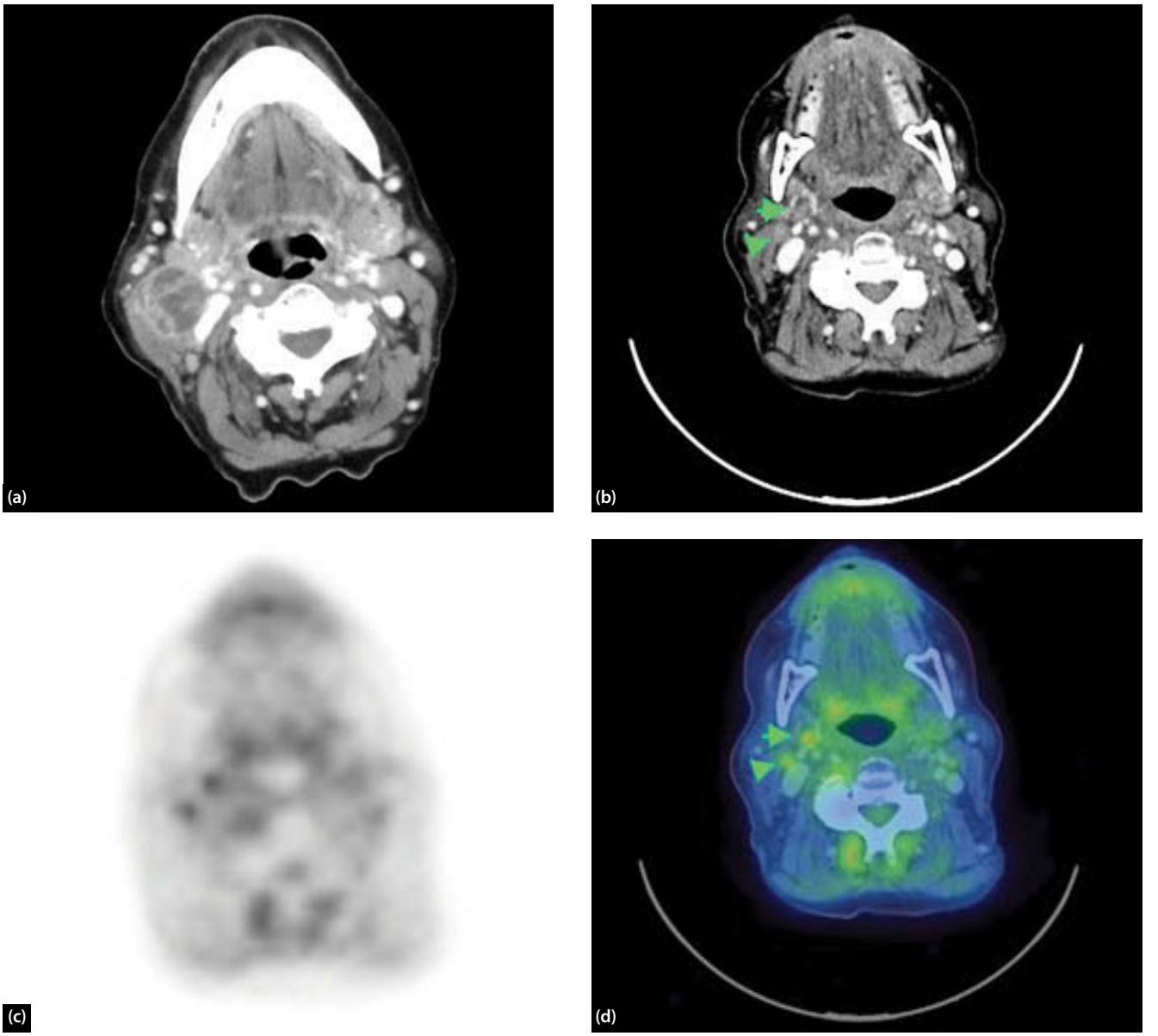

Figure 18.11 **(a)** The pre-treatment CT scan demonstrating a metastatic node in the right side of the neck. Post-treatment CT component of PET-CT scan **(b)** at 12 weeks shows small residual nodal swelling (green arrowheads). The PET **(c)** and the fused PET-CT **(d)** images show equivocal standard uptake values. The decision was made to follow up this patient without surgical intervention (Image courtesy Dr Tamir Ali, Newcastle upon Tyne Hospitals).

patients had disease beyond the clinically predicted single neck level. Only one of these patients would not have had their disease appropriately removed with a limited SND.

The timing of neck dissection after chemoradiation has not been systematically assessed. Nodes tend to regress at variable rates after irradiation. Bataini[168] suggested an interval of at least 8 weeks for nodes 6 cm and less and longer periods (16–20 weeks) for those more than 6 cm. Pathological studies have shown that metastatic disease can be demonstrated in 30% of necks after chemoradiation despite clinical and radiological evidence of complete response, but this does not correlate with the clinical outcome of low (5%) recurrence.[169–172] This may be due to non-viable cells and the fact that many of the neck dissections were done 4–6 weeks after treatment. The neck is best assessed between 8 and 12 weeks as discussed above and salvage offered following this. Surgical procedures on necks after chemoradiation necks are associated with more complications.

NECK DISEASE ASSOCIATED WITH HUMAN PAPILLOMAVIRUS

Enormous research interest lies in head and neck cancer caused by HPV, as it continues to increase in incidence in many parts of the world and as it represents a distinct type of head and neck cancer. The overwhelming majority of HPV-induced cancer is found in the oropharynx.

Most patients who present with HPV-induced OPSCC, do so with advanced disease, often with nodal metastases. Currently, there is no recommendation that HPV-induced OPSCC should be treated any differently to all other non-HPV-induced head and neck cancer with nodal disease. The recognition that patients with HPV-induced OPSCC have better survival outcomes has led some to question whether their management can be better tailored to reduce treatment-related morbidity, whilst maintaining treatment efficacy. As many patients with HPV-induced OPSCC present with small volume, discrete primary tumours, lacking field cancerization change, in combination with nodal metastases, there has been a growing interest in offering transoral surgery to these patients. However, the major stumbling block in offering transoral surgery over primary non-surgical management is the debate around management of the neck disease. Patients with HPV-induced OPSCC have a high rate of ENE within nodal metastases. Based on the current level 1 evidence, any patient with ENE found in their neck dissection, completed as part of their primary surgical management, should be offered adjuvant chemoradiotherpy.[33] There are arguments against such aggressive adjuvant therapy for this particular group of patients: whilst the evidence in support of adjuvant chemoradiotherapy is incontrovertible for ENE, especially for OPSCC, the data on which the conclusions are drawn are somewhat dated and may pre-date the rapid rise in HPV-induced OPSCC. As such, it is possible that only a minority of patients in the two RCTs had HPV-induced OPSCC.[136, 137] We have no data to demonstrate what the survival advantage may be for patients with HPV disease who receive chemotherapy in addition to adjuvant radiotherapy. A large multicentre study assessing the outcomes of transoral laser surgery in 204 patients with advanced stage OPSCC demonstrated no survival difference using multivariate analysis in those patients with or without ENE.[173] In this series, 74% had HPV-induced disease, 63% had ENE and only 16% received adjuvant chemoradiotherapy. A further study of patients undergoing primary surgery demonstrated that whilst ENE was an independent factor in disease-specific survival in oral cavity cancer, ENE did not affect disease specific survival in the 133 OPSCC patients (57% p16 positive). A phase II randomized trial is currently recruiting in the UK to assess the functional outcomes of a reduction in adjuvant therapy, prior to the proposed phase III study to assess survival, for patients with HPV-positive OPSCC treated with primary transoral surgery and neck dissection. Within this trial, patients with ENE are randomized to either adjuvant radiotherapy alone or adjuvant chemoradiotherapy.[174] A similar randomized trial is ongoing in the USA.[175]

TREATMENT OUTCOMES

Regional control rate in the pN0 neck is consistently good with failure rates between 3% and 7%, largely irrespective of the modality of treatment. Recurrence rates following therapeutic neck treatment will vary depending on other factors such as control of the primary site, ENE and the stage. Where the primary tumour has been controlled, overall recurrence rates range from approximately 10% for N1 disease without ENE, 20–30% for N2 disease and up to 85% for N3 disease although some small series quote better results,[1, 142, 176] In many cases of N3 disease, the primary site remains uncontrolled.[8]

Recurrent neck disease

Recurrence in the neck following previous treatment carries a poor prognosis. However, there will be instances in which further treatment is appropriate to control the disease and relieve symptoms, accepting the ultimate lack of curative intent. In accordance with the natural history of HNSCC, the majority of recurrences occur within the first 2 years of treatment. Various considerations including status of the primary site, extent and nature of recurrence, distant metastases and comorbidity dictate the treatment. Thus, a comprehensive investigation of the general status of the patient and distant metastases should be performed. Many of these masses will be fixed to vital structures which will negate extensive surgery. In patients who present with unresectable disease, re-irradiation with or without chemotherapy should be considered, particularly in those who present more than 2 years since their previous treatment. Evidence of partial repair of RT-induced spinal cord subclinical damage and newer RT delivery techniques (IMRT, tomotherapy, protons) that allow better sparing of neurological structures at risk make this a realistic option in a larger number of patients. If surgery is possible, wide resections should be undertaken and post-operative re-irradiation considered. About one-third of patients will be untreatable at presentation.

RECURRENCE IN THE IPSILATERAL UNTREATED NECK

In this situation, neck dissection is usually the preferred treatment with or without post-operative radiotherapy based on the histology. This group of patients do relatively well and local control rates between 50% and 60% can be expected. Alternatively, irradiation with surgical salvage may be used along the principles described above.

RECURRENCE IN THE CONTRALATERAL UNTREATED NECK

A proportion of patients in whom metastases occur on the untreated contralateral side of the neck sometime after a dissection on the other side may be salvaged, provided there is no recurrence at the primary site. In a retrospective review of 2550 patients, Spector et al[177] concluded that delayed metastases occurring on the untreated contralateral side were associated with significantly better salvage rates (42.5%) than the ipsilateral previously treated neck (17%).

RECURRENCE IN THE PREVIOUSLY TREATED NECK

Radical radiotherapy can be used if there is recurrent disease in the neck developing after previous surgery, which was not followed by post-operative irradiation. Owing to scarring from previous treatment, the neck stage is often N2a or more at presentation and ENE occurs in the vast majority of patients.

A multi-institutional review[178] studied 77 patients with cervical recurrence on the treated side, in the setting of a controlled primary. The review found that attempting salvage was useful in selected patients, giving a 33% control rate at 3 years. Results were better when surgical salvage was performed, but this probably reflects the low disease volume. Salvage rates were significantly better in the previously irradiated neck rather than the neck treated by previous surgery, with disease-free intervals being 46 months and 8 months respectively. The use of a pedicled pectoralis major flap or free flap should be seriously considered when embarking on salvage neck dissection, to reduce wound healing complications.

NODAL RECURRENCE AFTER COMBINATION TREATMENT

The prognosis is extremely poor in those patients who suffer a neck recurrence following previous surgery and radiotherapy, with median disease-free intervals of 4 months.[178] This clinical situation is often associated with distant metastases. However, the presence of such disease in the neck causes distressing symptoms such as pain or bleeding, together with offensive fungation and in selected cases further treatment may be appropriate. This includes wide excision of the tumour and the overlaying skin, flap reconstruction and brachytherapy. In very selected cases, re-irradiation may be an option. Evidence of partial repair of RT-induced spinal cord subclinical damage and newer RT delivery techniques (IMRT, tomotherapy, protons) that allow better sparing of neurological structures at risk make this a realistic option in a larger number of patients.

IMPACT OF NECK TREATMENT ON QUALITY OF LIFE

The issues that relate to quality of life (QOL) and the treatment of metastatic neck disease are discussed below.

Elective surgery versus irradiation of the N0 neck

There are no studies comparing (QOL) between these two treatments and there is very little morbidity associated with a well-executed SND. This is because vital structures are preserved and level V is not usually dissected. In contrast, a strategy of uniformly irradiating both sides of the neck to try and decrease the likelihood of occult cancer growth may be associated with numerous problems since radiation does not always control occult neck cancer, the fate of recurrent cancer in an electively irradiated neck is much more difficult to salvage and isolated recurrence in the contralateral neck is extremely unlikely.[8] In addition, treatment options for second primary tumours are diminished when wide-field radiotherapy has been applied to both sides of the neck and there are no prospective randomized studies which demonstrate a survival disadvantage when the N0 neck is observed. In summary, the QOL issues relating to elective irradiation appear less transparent than those for elective surgery and should not be underestimated when prescribing its use. Further studies are awaited.

Impact of neck treatment on the shoulder

Neck surgery for node positive disease usually involves a 5-level dissection and there are QOL issues that relate both to the extent of the dissection and which tissues are sacrificed (i.e. accessory nerve, sternomastoid muscle and the internal jugular vein). Shoulder problems are greater in patients undergoing a RND as opposed to a MRND.[179, 180] Despite preserving the accessory nerve in MRND, dysfunction occurs due to the nerve being devascularized and stretched. The least problems are seen in patients undergoing an SND.[98] It is noteworthy that SNDs that clear levels II– IV can also affect the shoulder by stretching the accessory nerve during dissection of the submuscular recess (level IIb).[181] Quite clearly if level V is not dissected, this may improve QOL. However, it must be noted that the trade-off for not dissecting all five levels may be the subsequent morbidity of post-operative radiotherapy, which does contribute to shoulder dysfunction.[126]

The use and extent of radiotherapy to the neck

While the effects of neck surgery are confined to the neck, radiotherapy fields often include the salivary glands and some of the viscera, leading to side effects such as mucositis and xerostomia. Use of intensity-modulated radiation therapy (IMRT) has allowed parotid-sparing techniques. Results from randomized controlled trials indicate that IMRT does improve quality of life, at least in the early years.[182] In addition, the evidence that both sides of the neck need to be irradiated in well lateralized primaries post-operatively is flimsy since the incidence of contralateral neck disease is relatively uncommon in certain tumours, as discussed earlier.[8] Unfortunately, many oncologists continue to routinely prescribe bilateral post-operative radiotherapy to the neck.

In our efforts to improve quality of life and reduce the traumatic psychosocial impact, a number of specialist centres are now in the process of balancing science with ethics and the human experience with a surge of QOL research and, hopefully, an evidence-based rationale to guide us in the future. Until a major therapeutic breakthrough takes place, reducing physical treatment morbidity, improving patients' overall QOL and minimizing the psychosocial impact of therapy will continue to present our greatest challenge in the practice of head and neck surgery.

FUTURE RESEARCH

The quality and quantity of randomized trials for metastatic neck disease is acknowledged to be limited, but this has improved significantly in recent years. Particularly in the UK, the improved structure of research trial coordination has led to the successful completion of a number of surgical trials, most notably the PET-NECK trial. As a result of this successful trial a number of clinical trials have been funded and are now recruiting well. Further research should involve the integration of modified randomized trials with prospective audit and quality control studies.[183] The following are areas where further work needs to be addressed.

- Imaging of low volume disease
- Significance of occult cancer in the neck
- Molecular detection of occult neck disease and its significance
- Sentinel node biopsy for occult neck cancer, in non-oral cavity cancer
- Selective neck dissection for palpable disease
- Superselective neck dissection for residual disease after chemoradiation
- Management of the contralateral neck
- Quality of life should be investigated following various treatment modalities
- Centralization with specialization and appropriate data collection should improve research, audit and quality control.

KEY POINTS

- Head and neck squamous cell cancer is a systemic disease.
- Tumour-host interaction has a major role to play in the outcomes of treatment.
- Metastatic cervical lymphadenopathy is the most important prognostic factor in head and neck squamous cell carcinoma.
- Patterns of neck metastases are altered by previous treatment.
- Subclinical neck disease is not early cancer.
- Selective neck dissection is adequate in the management of N0 necks.
- Elective neck dissection should be considered for all T1-2 N0 oral cavity SCC, and should be performed for tumours with a depth of over 3 mm.
- Modified radical neck dissection is as good as radical neck dissection in regional control.
- Adjuvant radiotherapy or chemoradiotherapy is indicated for surgically managed N2 and N3 disease and for N1 disease with poor prognostic features.
- Where there is access to it, PET-CT should be performed 12 weeks after primary chemoradiotherapy for N2 and N3 disease. The results should guide the need for subsequent neck dissection.
- In selecting treatment options, QOL issues are important considerations.

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CHAPTER 19

PRINCIPLES AND PRACTICE OF RADIOTHERAPY IN HEAD AND NECK CANCER

Sara Meade and Andrew Hartley

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SEARCH STRATEGY

Data in this chapter may be updated by a Medline Search using the following keywords: head and neck, radiotherapy, intensity-modulated radiotherapy, linear quadratic equation, therapeutic ratio and radiobiological modelling.

INTRODUCTION

Radiotherapy as a single modality or combined with synchronous chemotherapy is capable of high rates of tumour control. A local control rate of 90% at 5 years would be expected both when radiotherapy is administered as the sole treatment for a T1-glottic carcinoma and when HPV-associated oropharyngeal cancer is treated with synchronous chemoradiation in patients without a significant smoking history.[1–6]

However, these high rates of local control come at considerable cost to the patient. Acute side effects can include mucositis which often requires the use of strong opioid analgesia, taste disturbance, hair loss, acute xerostomia, dysphagia requiring the use of temporary tube feeding and skin reactions. Long-term side effects can include the risk of osteoradionecrosis, xerostomia and the risk of stricture formation and fibrosis necessitating long-term tube feeding. There is no strong evidence that prophylactic treatment of these side effects is effective other than the use of intensity modulated radiotherapy to avoid late xerostomia.[7–10] On the contrary an adverse effect on local control was observed in one study when patients were randomized to receive prophylactic granulocyte-colony stimulating factor (G-CSF) during irradiation with no improvement in the rate of acute mucositis, a finding with possible implications for prophylactic G-CSF use during chemoradiation.[11] Death during or within 8 weeks of completion of treatment, when actually reported in randomized trials, occurs in 0–7% of patients undergoing radiotherapy alone and 0–14% with chemoradiation. Deaths definitely ascribable to treatment are reported in 0–3% and 0–5% of patients respectively.[11–23]

It is therefore essential that this therapeutic ratio i.e. the benefit to the patient (altered chance of cure) vs the detriment to the patient (altered chance of mortality/morbidity) is considered in detail when any modification to the radiotherapy or chemoradiotherapy schedule is made.[24–28] In this chapter the physical, chemical and biological processes involved in radiotherapy delivery will be briefly considered to enable an appreciation of the way in which these processes have already been or may be modified in the future to affect this ratio. The radiobiological modelling of such modifications will then be considered.

Basic physical, chemical and biological processes

Photons for use in head and neck radiotherapy, normally of energy of 6 megavolts (MV), are produced in a linear accelerator by accelerating electrons into a target. The photon beam produced can be shaped by using a series of collimators in the head of the machine (multi-leaf collimators) which are able to move permitting intensity-modulation between the delivery of multiple beamlets (step and shoot

intensity-modulated radiotherapy (IMRT)) or during the delivery of the beam (dynamic IMRT). The gantry of the linear accelerator can also move around the head of the patient to deliver photons from different beam angles. If the IMRT is only delivered while the gantry is stationary from a number of set-beam angles (normally 5 or 7 in head and neck IMRT) the treatment is known as fixed-beam step and shoot IMRT. If the IMRT is delivered while the gantry is rotating about the patient the treatment is known as dynamic arc IMRT.[24, 29, 30] Intensity Modulated Proton Therapy (IMPT) may be considered in the future for certain head and neck tumours due to the ability to reduce the 'low dose bath' with this modality (**Figure 19.1**).

Photons cause ionization in normal tissue resulting in the formation of secondary electrons which cause further ionization resulting, in the presence of oxygen, in free-radical formation. The principal target of radiotherapy at a cellular level is deoxyribonucleic acid (DNA). Radiation causes cell death primarily through single- or double-strand breaks in DNA. Single-strand breaks are mostly due to the effects of hydroxyl radicals (OH^-) formed as described above. Double-strand breaks are directly proportional to the dose of radiation delivered and may result from direct interaction by the photons or secondary electrons with the DNA double strand.[31–34]

In general it is the double-strand breaks that are crucial for the lethal effects of radiation. Irreparable DNA damage causes sterilization of the tumour cell with loss of proliferative capabilities, also known as cell kill.[35] However, single- and even double-strand breaks can be repaired by complex repair processes.[36, 37] It must be remembered that both tumour cells and the varied normal tissues which surround the tumour are affected by radiation. It is the differential response between tumour and normal tissues in their ability to repair DNA lesions and their response to the amount of radiotherapy delivered per treatment (fraction size) which the head and neck radiation oncologist utilizes in order to maximize the therapeutic ratio.[25]

Radiobiological modelling

There have been many randomized studies of altered fractionation in head and neck cancer and thus it has been possible to test in the clinical setting models of tumour cell kill and normal tissue response originally derived from the irradiation of cell lines.[38–45] An understanding of the relatively straightforward calculations involved in such modelling together with an appreciation of the limitations of such models is essential for radiation oncologists and helpful for other members of the multidisciplinary team.

Linear quadratic equation and biologically effective dose (BED)

Since 1989 the linear quadratic equation and the concept of BED has been proposed as a model for comparing the biological effects from different dose schedules in radiotherapy:[46–49]

$$E = \alpha nd + \beta nd^2$$

Where:

- E = biological effect
- n = number of fractions of radiotherapy in a course
- α = linear component of cell kill or intrinsic radiosensitivity or lethal hit component of cell kill in units of $Gray^{-1}$ (Gy^{-1}). One Gray (Gy) is equivalent to 1 Joule of energy deposited per kilogram of tissue.
- β = quadratic component of cell kill or component of cell kill resulting from combined sublethal hits in units of Gy^{-2}
- d = dose per fraction

In the mode of action of radiotherapy discussed above the alpha component of cell kill might be considered to be related to the number of double-strand breaks and the beta component related to the number of combined single-strand breaks. The beta component is inversely

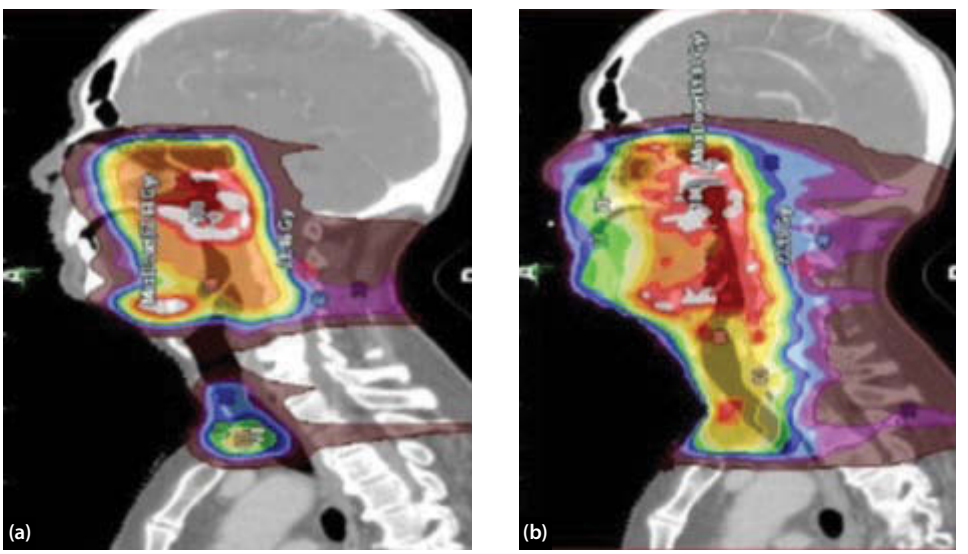

Figure 19.1 Sagittal plane of **(a)** an Intensity Modulated Proton Therapy (IMPT) plan and **(b)** an Intensity Modulated Radiotherapy (IMRT) plan illustrating potential sparing of the posterior fossa of the brain and posterior cervical musculature (Images courtesy of Mr. Trevor Williams).

proportional to the repair ability of the tumour or tissue under consideration. To make this model useful clinically, the concept of BED has been defined. This permits the comparison of different dose fractionations. Two different dose fractionations which result in the same specific biological effect in a defined tissue (which might be a particular tumour or normal tissue) will have the same BED.[46]

BED is derived by dividing the above equation by the intrinsic radiosensitivity parameter alpha:[46–48]

$$\frac{E}{\alpha} = BED = \frac{\alpha nd}{\alpha} + \frac{\beta nd^2}{\alpha} = nd + \frac{\beta nd^2}{\alpha} \tag{19.1}$$

Factorizing gives:

$$BED = nd\left(1 + \frac{\beta}{\alpha}d\right) = nd\left(1 + d\Big/\frac{\alpha}{\beta}\right) \tag{19.2}$$

Number of fractions (n) times the dose per fraction (d) = D = total dose:

$$BED = D\left(1 + d\Big/\frac{\alpha}{\beta}\right) \tag{19.3}$$

Where $\frac{\alpha}{\beta}$ is known as the alpha beta ratio and reflects the sensitivity of different tumours or normal tissues to changes in the dose per fraction d or fraction size. For example the $\frac{\alpha}{\beta}$ for squamous cell carcinoma of the head and neck is considered to be around 10 Gy and for the acute musocal reaction seen during radiotherapy also around 10 Gy but for late mucosal damage around 3 Gy.[50–52] From the above equations, it can be seen that the lower the $\frac{\alpha}{\beta}$ of the tissue the greater the sensitivity to changes in fraction size.

If two treatment regimes used for squamous carcinomas, 55 Gy in 20 fractions (#) and 70 Gy in 35# are considered in terms of likely late mucosal toxicity it is possible to calculate the BED for late mucosal toxicity for both regimes using equation 3. In this example it is necessary to use an $\frac{\alpha}{\beta}$ of 3 Gy. For the first regime with total dose (D) of 55 Gy and dose per fraction (d) of 2.75 Gy, the BED is 105 Gy. For the second regime with D = 70 Gy and d = 2 Gy the BED is 117 Gy i.e. higher rates of late mucosal damage might be expected with the second regime. Although there is a higher dose per fraction in the first regime, the decreased total dose offsets this. In calculations such as these the BED may be reported as $105\,Gy_3$ and $117\,Gy_3$, the subscript reflecting that the dose has been calculated using an $\frac{\alpha}{\beta}$ of 3.[53, 54]

Equivalent dose in 2 Gy fractions (EQD2)

Often BED is converted into equivalent dose in 2 Gy fractions (EQD2) as in the conformal era normal tissues and tumours often received a homogenous dose. Therefore, radiation oncologists were used to working with both tumour doses and normal tissue tolerance in 2 Gy per fraction.[47, 51, 52, 54] This is less relevant in the IMRT era as both total doses and dose per fraction differ greatly between tumour and normal tissues. If needed the conversion can be made:

$$EQD2 = \frac{BED}{\left(1 + 2\Big/\frac{\alpha}{\beta}\right)} \tag{19.4}$$

A similar calculation can be performed for the response of tumour using an $\frac{\alpha}{\beta}$ of 10 Gy. For the two regimes considered above this results in tumour BEDs of $70\,Gy_{10}$ and $84\,Gy_{10}$ and EQD2s of $58\,Gy_{10/2}$ and $70\,Gy_{10/2}$ (the subscripts now indicating that the calculations have been made for a tissue (in this case a tumour) of $\frac{\alpha}{\beta}$ of 10 Gy but that the dose is quoted as if it were delivered in 2 Gy fractions).

The effect of time on biologically effective dose

From the above calculation it would be expected that the second regime (70 Gy in 35) would be associated with a higher rate of tumour control but, in reality, control rates seen with these regimes are similar. In several studies prolonging the overall treatment time over which a fractionated course of radiotherapy is delivered for squamous cell carcinoma of the head and neck results in reduced tumour control.[55–58] This is thought to occur due to an increase rate of cell proliferation in surviving cells once radiotherapy has commenced. In most recent radiobiological studies this accelerated repopulation is modelled to commence at around 21 days known as the kick off time or T_k.[58–62] For squamous cell carcinoma during radiotherapy, the cell turn over time or T_p is modelled at 3 days. A modified equation for BED to take into account overall treatment time has been derived for overall treatment time (T):[51–52]

$$BED = D\left(1 + d\Big/\frac{\alpha}{\beta}\right) - \left(\frac{\ln 2}{\alpha} * \frac{(T - T_k)}{T_p}\right) \tag{19.5}$$

Repeating these calculations for the two regimes above having T of 25 days and 46 days respectively, using a value for alpha of $0.3\,Gy^{-1}$, gives BEDs of $67\,Gy_{10}$ and $65\,Gy_{10}$ suggesting more similar tumour controls. The reliability of these models for tumour control will be discussed in 'Altered fractionation' below.

Such calculations are useful not only in the design of randomized studies but for devising revised schedules when an unintended gap in treatment occurs.[63–66] Such gaps should be avoided where possible but may be compensated for by altered fractionation following the gap. It is important to note that for late side effects such as late mucosal damage or neurological damage there is no correction for time when calculating BED. Late responding tissues appear dependent on total dose and fraction size only and typically have a low $\frac{\alpha}{\beta}$ ratio.[67]

The same calculations as performed for tumour can be performed for BED with respect to the rate of acute grade 3 ucosal reactions which has been considered the dose limiting acute toxicity in head and neck cancer. Tolerance models for the acute mucosa for different radiotherapy schedules have been devised.[50, 68, 69] When calculating BED for acute mucosa the values for $\frac{\alpha}{\beta}$, α, T_p and T_k used are 10 Gy, 0.35 Gy^{-1}, 2.5 days and 7 days. In the simplest of three published models based on published studies of radiotherapy as sole modality in head and neck cancer, Fowler et al. suggest that schedules with an acute mucosal BED (amBED) greater than 61 Gy_{10} were unlikely to be tolerable due to severe acute mucositis.[51] Such models should again inform the design of future randomized studies although it is important to note that they are based on data from the conformal era and that mucosal sparing achievable with IMRT or IMPT may not be taken into account.[70, 71] A recent study has suggested that these tolerance models may be used in the chemoradiation setting (**Figure 19.2**).[72]

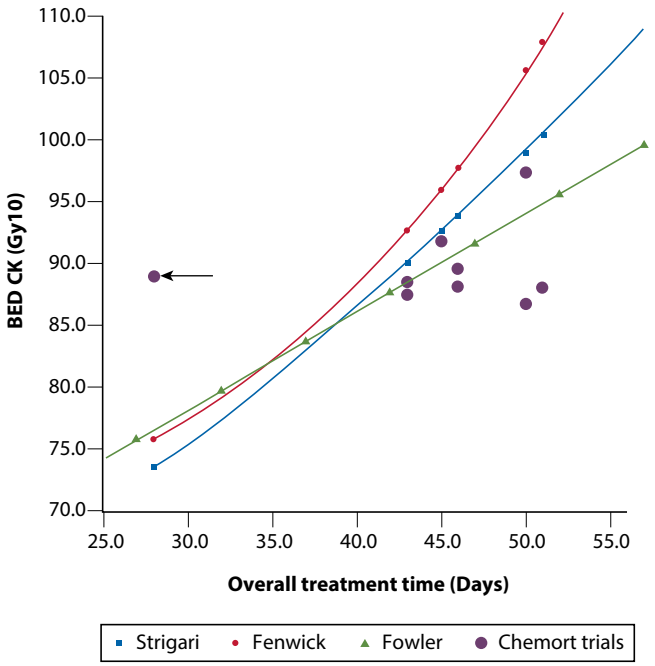

Figure 19.2 Plot of biological effective dose cell kill (BED CK) including contribution from chemotherapy against overall treatment time to illustrate how radiobiological modelling can predict mucosal tolerability. The arrowed trial is predicted to be above the levels of tolerability of 3 published models and indeed was shown to have a grade 3–4 mucositis rate of 77%.

CLINICAL PROCESS FOR A PATIENT UNDERGOING CHEMORADIATION FOR HEAD AND NECK SQUAMOUS CELL CARCINOMA

Radiotherapy for head and neck cancer offers numerous possibilities for modifications to the treatment schedule which might affect the therapeutic ratio. Before considering these and the ways in which their effect might be modelled, a typical patient pathway will be outlined. If the example of a locally advanced squamous carcinoma with p16 positivity invading the base of tongue to midline with no neck nodes or distant metastases in a patient without a significant past smoking history is taken, this patient might expect to be treated in the following way:

Preparation: The patient's case will have been discussed in a multidisciplinary meeting with surgeons, radiation oncologists, histopathologists, radiologists, dieticians, speech therapists and clinical nurse specialists present. The acute and late side effects of the treatment would be discussed with the patient and the patient would give consent. The patient would be offered a choice between having a prophylactic or a reactive feeding tube placed. Dental assessment would be arranged.

Immobilization: The patient's head and shoulders would be immobilized in an immobilization device known as a shell or mask which is subject to regular departmental audit. The data from such audit would be used to inform the planning target volume (PTV) margins below.

Imaging: The patient would have 2 mm slice CT scanning with intravenous contrast in the immobilization device with diagnostic MRI imaging fused to these images.

Target volume definition: The head and neck radiation oncologist would define the GTV based on MRI and CT. A small margin to allow for microscopic spread and the limitations of fusion and the imaging employed (5–10 mm) would be added to form the high-dose clinical target volume (CTV) to receive 70 Gy in 35 fractions. Adjacent areas of oropharynx and nodal regions felt to be at high risk of harbouring microscopic disease may be included in a prophylactic CTV to receive 56 Gy in 35 fractions. PTV margins based on in-house data derived from audit of image guided radiotherapy (IGRT) normally 3–5 mm are added to both CTVs.

Organs at Risk definition: The minimum organs at risk defined for a case such as this would include the spinal cord, brainstem, contralateral parotid, brain and mandible. Other organs that might be contoured but constraints would normally be achieved with ease include lens, optic nerves, chiasm. Other volumes which may be contoured in an attempt to reduce toxicity include oral mucosal volume, laryngeal framework, brachial plexi, cochlea and swallowing muscles.

Peer review of contours: The CTV defined by the radiation oncologist should where possible be peer reviewed particularly in complex cases (skull base, post-operative and following neoadjuvant chemotherapy).

Treatment planning: The departmental dosimetrists would produce an IMRT plan which is reviewed quantitatively and qualitatively by the radiation oncologist and then subjected to rigorous quality assurance.

Delivery: The above plan would be delivered over 7 weeks (number of treatment days 35 but overall treatment time 46 days). Each day the patient would be imaged using cone

beam CT scanning or megavoltage imaging to check positioning and assess any changes in contour due to weight loss or tumour shrinkage which might affect dosimetry (IGRT).

Chemotherapy: Provided the patient was less than 70 and there were no contraindications the patient would receive cisplatin 100 mg/m^2 on the Monday of week 1, 4 and 7 of radiotherapy.

Supportive care: The patient would be reviewed weekly during treatment and till the mucosal reaction has settled by a multidisciplinary team of radiation oncologist, radiographers, speech therapists, dieticians and nurses.

At nearly every point of the example pathway described above there are alternatives or points of controversy. Many of these will be discussed in detail in other chapters. From the literature it is clear that for the most fundamental component of radiotherapy delivery, target volume definition, there is considerable heterogeneity between clinicians.[73, 74]

Altered fractionation

As an illustration of how the linear quadratic model can be used both to model changes in the therapeutic ratio and to clarify terminology associated with radiotherapy fractionation schemes, altered fractionation as an alternative to chemoradiation will be considered.

Although 70 Gy in 35 fractions (overall treatment time 46 days (7 weeks)) has been defined as the standard above, prior to chemoradiation being accepted as standard treatment several different fractionation schemes had been the subject of randomized studies.[39–45] In describing such schemes certain definitions need to be understood. Acceleration is a reduction in the overall treatment time below the standard 46 days. Hyperfractionation is the use of less than 2 Gy per fraction. Conversely hypofractionation is the use of more than 2 Gy per fraction. Dose escalation is an increase in the total physical dose above 70 Gy. The schedules tested in randomized trials include hyperfractionated dose escalated schedules e.g. 84 Gy in 70# over 46 days with 2 fractions delivered twice a day. In this case, dose escalation is made possible because the fraction size is reduced and thus late side effects which depend only on total dose and dose per fraction are not enhanced (late BED for 84 Gy in 70# is 118 Gy_3; for 70 Gy in 35# is 117 Gy_3 (equation 3). Other examples include pure accelerated schedules e.g. 68 Gy in 34# delivered over 38 days (DAHANCA schedule) where the total dose is only dropped minimally and overall treatment time is reduced.[43] Finally, very accelerated schedules were tested such as the CHART regime 54 Gy in 36 fractions over 12 days where 3 fractions a day were administered over 12 continuous days (no weekend breaks).[41] To make very accelerated regimes tolerable to the acute mucosa it was necessary to drop the total dose. A meta-analysis of trials of altered fractionated grouped trials into these three groups as described above and found that an overall survival benefit was only found in the hyperfractionated dose escalated group.[38, 75] This survival benefit is approximately the same as that seen with the addition of synchronous chemotherapy to standard radiotherapy. Unfortunately, this benefit was not seen in patients aged over 70 and so dose-escalated hyperfractionated radiotherapy is not an evidence based alternative to chemoradiation in this cohort.

Using the randomized trials considered in this meta-analysis, one study has shown a strong correlation between BED calculated for each regime using the parameters described above and the proportional change in local control, rate of acute grade 3 mucositis and late mucosal damage seen between study arms.[67] Studies indicate a 1.2% change in local control for a 1% change in BED in the dose range considered. This finding supports the use of the linear quadratic equation as a guide to predicting both tumour and toxicity endpoints in radiotherapy studies.

The therapeutic ratio: dose-escalated radiotherapy or synchronous chemoradiotherapy

The addition of synchronous chemotherapy to radiotherapy has been associated with an 8% survival advantage.[76] As the same benefit can be achieved with dose escalation of radiotherapy alone, modelling studies have looked at the effect on the therapeutic ratio of the addition of synchronous chemotherapy.[24, 77, 79] Initially such studies calculated the effect of chemotherapy on local control as an additional radiotherapy dose in terms of BED using knowledge of the dose response. Such studies suggest that the addition of chemotherapy to radiotherapy is equivalent to the addition of three–four 2 Gy fractions in terms of local control.[24, 77–79] A similar calculation can be performed for the rate of grade 3 mucositis and an approximate mucosal sparing of two 2 Gy fractions for the use of synchronous chemotherapy rather than dose escalated hyperfractionated radiotherapy was proposed.[24] That is, synchronous chemotherapy is beneficial to the therapeutic ratio if the principal benefit of local control and the principal dose limiting side effect of grade 3 mucositis are considered.

However, two recent trials of accelerated fractionation chemoradiation versus conventional fractionation chemoradiation have cast doubt on such modelling.[80, 81] In both these studies the expected increase in local control with accelerated chemoradiation predicted both by previous radiobiological modelling and meta-analysis was not observed.[82] One hypothesis for the lack of benefit for acceleration in these studies is that accelerated repopulation may be compensated for by synchronous chemotherapy. Alternative modelling has been proposed where the dose lost from accelerated repopulation is reduced when synchronous chemotherapy is used by increasing the value of T_p for both tumour and mucosa in equation 19.5 above.[83, 84] Interestingly, a therapeutic loss is predicted for the addition of chemotherapy when this modelling is employed.

While the above serves as an example of how radiobiological modelling can be employed, such an analysis of the therapeutic ratio is limited as it ignores overall survival and the many other early and late toxicities experienced

by patients. It is also largely based on data from the conformal radiotherapy era and toxicity sparing from IMRT is not taken into account.

CONCLUSION

A basic understanding of the mechanism of action of radiotherapy, the radiotherapy preparation and delivery process, the linear quadratic equation and the rationale for the use of chemoradiation or altered fractionation radiotherapy as described above can be beneficial to all members of the multidisciplinary team treating head and neck cancer patients.

KEY EVIDENCE

- Parotid sparing radiotherapy reduces late xerostomia.
- Dose-escalated hyperfractionated radiotherapy increases overall survival by 8% at 5 years compared with conventionally fractionated radiotherapy alone.
- The addition of synchronous chemotherapy to radiotherapy increases survival by 8% at 5 years compared with conventionally fractionated radiotherapy alone.
- Two randomized trials have failed to show evidence for a survival benefit of synchronous chemotherapy and accelerated radiotherapy over synchronous chemotherapy and conventionally fractionated radiotherapy.

KEY POINTS

- Prolonging the overall treatment time reduces the efficacy of radiotherapy.
- The Linear Quadratic Equation can be used to predict the results from future randomized studies.
- The Linear Quadratic Equation can be used to devise compensation schedules following unscheduled gaps in radiotherapy.

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CHAPTER 20

QUALITY OF LIFE AND SURVIVORSHIP IN HEAD AND NECK CANCER

Simon Rogers and Steven Thomas

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SEARCH STRATEGY

Data in this chapter may be updated by a Medline search using the keywords: Quality of Life, head and neck cancer, patient reported outcomes, questionnaires and survivorship.

INTRODUCTION

The aim of this chapter is to outline important aspects of quality of life and survivorship following head and neck cancer. The chapter is divided into five sections that take the reader from the definition and measurement of quality of life through to survivorship.

There are two million people living with or beyond cancer in the UK. This figure is set to rise to four million by 2030. It is a cause for celebration that more people than ever are surviving after diagnosis, but we know the impact of cancer does not suddenly stop when treatment is over.[1] There is considerable focus on survivorship through programmes such as the National Cancer Survivorship Initiative – improving the ongoing services and support for those living with and beyond cancer.[2] Survival is improving following oral cancer[3] and with advances in medical care, refinements in treatments and changes in the clinical characteristics of head and neck cancer patients, improved survival is expected in head and neck cancer (HNC) patients. Survivorship focuses on the health and life of a person with cancer from the completion of treatment until the end of life. It covers the physical, psychosocial, and economic issues of cancer, beyond the diagnosis and treatment phases (**Figure 20.1**). Survivorship includes issues related to access to healthcare and follow-up treatment, late effects of treatment, second cancers, and quality of life. It is recognized that family members, friends and caregivers are also part of the survivorship experience.[4] Quality of life

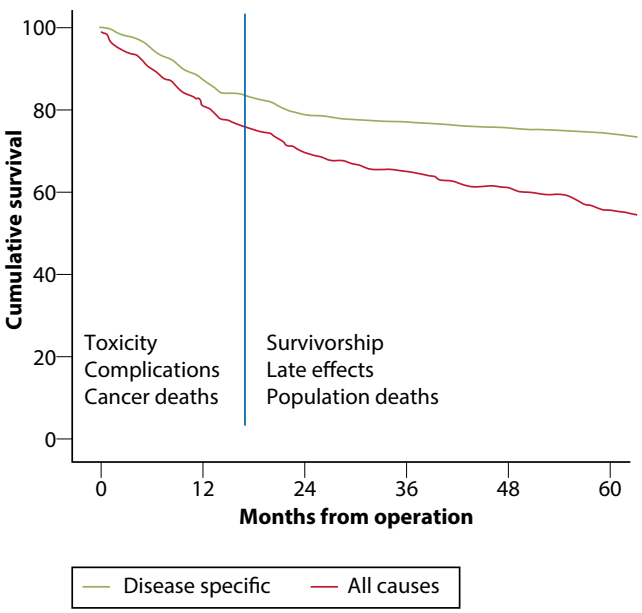

Figure 20.1 Transition from early post-treatment to longer term survivorship following HNC.

(QoL) for HNC patients is a crucial field in which interest has developed in the last two decades and there is now a considerable body of information available to clinical teams concerning QoL outcomes. There are several review articles summarizing the issues related to QoL.[5–9]

WHAT IS HRQoL AND HOW IS IT MEASURED?

Quality of life (QoL) is considered as a multidimensional concept. The World Health Organisation (WHO) defines quality of life as an '*individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns*'.[10] QoL is present in both the positive and negative aspects of different life domains. There are different theoretical models to help explain how QoL is constructed (**Figure 20.2**).[11, 12] In a simplistic model, cancer and its treatment has a consequence. The detrimental extent of this 'consequence' has a direct bearing on 'quality of life', for example, loss of tongue function after surgery or dry mouth following radiotherapy. How patients respond to that 'consequence' has many influences such as their ability to adapt and cope; however, the perceived consequence will influence the patient's ability to accept the situation. This has a direct bearing on their experienced QoL. Finally, in this theoretical model the patients' sense of cure and control over the cancer will impact on their perception of QoL. Hence, if patients are cured this has a positive impact on their QoL.

Health-related quality of life (HRQoL) is regarded as a subcategory of QoL and its coverage can be categorized into four areas related to physical functioning, psychological functioning, social functioning and symptoms from the disease and treatment.[9] The cross-cultural aspects and wide applicability of HRQoL has resulted in the availability of various validated translation questionnaires. Translations have to be carefully undertaken as it is possible that words or phrases differ between languages and cultures.[13] HRQoL is not usually considered to include expected acute toxicity.

HRQoL should not be limited to an outcome in research, but should make a vital contribution in the treatment and management careplan involving both patients and healthcare professionals.[8] HRQoL has a major role in treatment decisions in several but not all situations. For example, when different treatments have a good chance of cure, HRQoL will influence decison-making. The priority given to the best chance of cure often outweighs HRQoL outcomes for indiviual patients, treatment protocols and trial designs. Patients set cure and survival as priority and there is individual patient variability related to the side effects of treatment.[14–17] Another area where HRQoL has an important role is when treatments have equivalent survival outcome but the HRQoL outcomes are different. There might be a trade off with the degree of dry mouth, trismus, pain and swallowing difficulties depending on the modality of treatment used. Also, when the cancer treatment is very unlikely to be curative or the intention of treatment is palliative, there is a strong focus on treatments that maintain HRQoL for the remaining time available. Finally, some treatments result in such a poor HRQoL that even if cure is possible, the adverse impact on the patient HRQoL is too great to consider such treatment. Studies show that long-term survivors of advanced HNC accept major surgical procedures, with over 90% of 273 patients stating that 'I would undergo the same treatment'.[18] There is also strong agreement between patients, their companions and members of the multidisciplinary team (MDT) with regards to priorities in HNC outcomes and low post-treatment regret for patients and their companions. These results suggest that the patients' companions and members of the MDT are able to exercise good judgement when it comes to supporting patients in decision-making.[17] In spite of the enormity of the diagnosis and treatment, relatively few patients feel that they regret treatment. This, of course, may not reflect the reality of the personal experience that can be hidden from the healthcare profession.

HRQoL is usually measured by a patient's self-completed questionnaire. Questionnaires can be complemented by objective measures such as swallowing, speech and shoulder movments. There is no gold standard questionnaire that is best.[7, 19] The choice of questionnaire will depend on the context in which it is being used, based on the hypothesis being tested, such as general cancer issues (pain, depression), HNC-specific items (shoulder, appearance) or function-specific assessment (xerostomia, swallowing, speech).[20] **Table 20.1** gives common examples of the different questionnaires by group. The choice of questionnaire will be influenced by whether they are used in audit or research. The British Association of Head and Neck Oncologists and the British Association of Otorhinolaryngologists Head Neck Surgeons both recommend that HRQoL should be longitudinally recorded. Questionnaires are one of the ways to measure HRQoL and give a structured insight into the patients' point of view.[21] The most commonly used questionnaires[22] are the European Organization for Research and Treatment for Cancer (EORTC),[23] and the University of Washington quality of life (UW-QoL).[24]

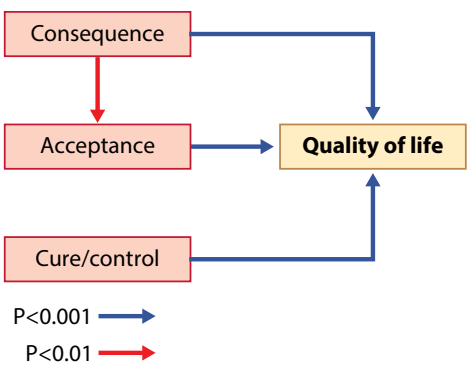

Figure 20.2 Theoretical framework: the interaction between the consequences of treatment and QoL.

TABLE 20.1 Examples of HRQoL questionnaires (Handle-On-QoL)

Group	Questionnaire name	Reference
General	EQ-5D	https://euroqol.org/eq-5d-instruments/eq-5d-5l-about/
General cancer	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30)	http://groups.eortc.be/qol/eortc-qlq-c30
	Functional Assessment of Cancer Therapy (FACT)	http://www.facit.org/facitorg/questionnaires
Head and neck cancer specific	EORTC H&N 35 and QLQ-H&N43 revision	http://groups.eortc.be/qol/eortc-qol-module-head-and-neck-cancer-qlq-hn43-revision-eortc-qlq-hn35
	FACT	http://www.facit.org/facitorg/questionnaires
	University of Washington Quality of Life Questionnaire (UWQOL)	http://www.hancsupport.com/professionals/quality-life/qol-questionnaires/university-washington
H&N cancer function specific	Voice related QOL (VRQOL)	Hogikyan ND, Sethuraman G. Validation of an instrument to measure voice-related quality of life (V-RQOL). J Voice 1999;13:557-69.
	MD Anderson Dysphagia Inventory MDADI	Chen AY, Frankowski R, Bishop-Leone J, Hebert T, Leyk S, Lewin J, Goepfert H. The development and validation of a dysphagia-specific quality-of-life questionnaire for patients with head and neck cancer: the M. D. Anderson dysphagia inventory. Arch Otolaryngol Head Neck Surg. 2001 Jul;127(7):870-6.
	Sydney Swallow Questionnaire (SSQ)	Dwivedi RC, St Rose S, Roe JW, Khan AS, Pepper C, Nutting CM, et al. Validation of the Sydney Swallow Questionnaire (SSQ) in a cohort of head and neck cancer patients. Oral Oncol 2010;46(4):e10-4.
	The London speech evaluation (LSE) Scale	Dwivedi RC, Rose SS, Chisholm EJ, et al. Development and validation of first-ever speech-specific perceptual speech evaluation tool for patients with head and neck cancer: The London speech evaluation (LSE) Scale. Head Neck 2012; 34(1): 94–103.
Other	Hospital Anxiety and Depression Scale (HADS)	Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand. 1983 Jun;67(6):361-70.
	Beck Depression Inventory (BDI)	Beck AT, Ward C, Mendelson M. Beck Depression Inventory (BDI). Arch Gen Psychiatry. 1961 4 (6): 561–571.

TREATMENT DECISIONS AND OUTCOMES IN THE CONTEXT OF HRQoL AND SURVIVORSHIP

The epidemiology of HNC in the UK is changing. The oral cavity is now the most common subsite and there has been a 51% rise in human papillomavirus (HPV)-related oropharyngeal cancers between 1989 and 2006[25] (The HPV-related cancers appear to affect younger people and may respond better to chemoradiotherapy with or without surgery.[25, 26] Organ-preserving therapies are favoured for laryngeal cancer.[27] The choice of treatments available is also changing. These choices are informed by recommendations made in MDTs and following discussion with patients.[28] It is desirable that treatment decision-making should be shared between patients and doctors.[29] Shared decisions involve the doctor learning about the patient, in particular the extent of their understanding, their circumstances and ultimately their wishes, and the patient learning from the doctor about the nature of the treatment and the prognosis.[30, 31] The patient may have to make a decision early in their treatment path which could have important implications for their HRQoL.[32] Shared decision-making improves patients' satisfaction with the consultation, leading to better quality of life.[33–35] Related to shared decision-making is the process of informed consent where an autonomous person has understanding of the treatment and intentionally authorizes the proposed action.[36–38] The view of what a 'reasonable patient' might expect outweighs standards being set from a 'reasonable doctor's view point'.[39] The exchange of information underpins both informed consent and shared decision-making, and there is evidence that patients want detailed information on the effect treatment will have on survival and quality of life.[40] QoL may include specific issues such as the effect on speech and swallowing as well as general issues including pain, fatigue and anxiety.[15, 41, 42] Information needs to be defined by the individual patient and not by the diagnosis or treatment.[36–38, 43, 44] Too much information can result in reduced recall and anxiety, too little information and it is unlikely that patients will be able to reach understanding.[31] Healthcare professionals need to disclose a core set of information about a treatment.[43] The development of a core information set for informed consent will improve the effectiveness of these processes for both patients and doctors.

As with 'Core Disclosure Sets', there is an increasing need for the development of 'Core Outcome Sets' to

enable standardization of outcome reporting in clinical trials. These would define a minimum set of outcomes that should be measured in clinical trials for any given condition. The purpose of core outcome sets is to improve the quality of research by emphasizing the importance of including relevant stakeholders, especially patients, in decisions about which outcomes should be measured and reported and reducing reporting bias by clear definition of outcomes.[45] Outcomes used in clinical trials of head and neck HNC frequently focus on objective measures of function and survival outcomes, but little is known about which outcomes are important from the patients' and carers' perspective.[44] Prognosis research in cancer often fails to report suffering from symptoms, functional status and QoL. Mortality may not be the most important outcome to the patient, nor is it necessarily a good proxy for other outcomes. A range of outcome predictors should be considered: the social and healthcare environment, psychosocial factors and health behaviours as well as biological factors.[46]

HRQoL AND SURVIVORSHIP

The MDT need to be aware that some patients will tend to report a much worse HRQoL. These patients might be helped by additional support through treatment and into survivorship. The types of patients most at risk of poor HRQoL outcome are given in **Table 20.2**.[8,47] Poor HRQoL has been identified as an independent predictor of survival[48–50] but this association may be influenced by various cancer-related, personal, biological, psycho-behavioural, physical, lifestyle-related and social factors.[51]

The main inflences of HRQoL are site, stage and treatment.[5–9, 52] There are much smaller differences by age and gender and these tend to be item-specific such as appearance. Older patients cope remarkably well[53, 54] and with careful selection and support, their expectations are less than younger patients and they can adapt remarkably well to the deficits after cancer therapy. Younger patients can experience more negative impacts related to family, employment, finance, and the the gap between the reality of what they have as a consequence of the cancer and the hopes and expectations for their lives. However, patients' ability to adapt and cope cannot be underestimated.[55]

TABLE 20.2 Common factors associated with worse HRQoL outcomes

Alcoholism: Pre exiting comorbidity and poor coping mechansim
Age: Young patients have much more to lose in terms of life expectation, finance.
Combined treatments: Surgery and radiotherapy, Chemoradiotherapy
Deprivation: Lower socio-economic background
Personality: Negative, nihilistic
Pre-existing distress: Anxiety related conditions, mental health
Single: Lack of support
Site: Oropharynx and hypopharynx
Stage: Advanced disease
Unknown: What clinical experience gives clinicians

SITE

Thyroid

A better understanding of HRQoL following thyroid cancer has developed over recent years and thyroid cancer-specific questionnaires are now available.[56] Awareness of these specific determinants of HRQoL could help healthcare practitioners to provide better supportive care. Long-term thyroid cancer survivors experience more symptoms and deteriorated HRQoL compared to the normative population. Thyroid cancer-specific neuromuscular, sympathetic, concentration and psychological symptoms are stronger associated with HRQoL than clinical and sociodemographic factors alone.[57]

Surgical, radiotherapy and hormonal aspects have been considered.[58–61]

Oral cavity

In most institutions, oral cancer tends to be treated by primary surgery. Conventional surgery with or without adjuvant treatment gives better HRQoL across most domains compared to chemoradiotherapy for oral cavity squamous cell carcinoma[62] including those issues considered most important to patients: chewing, swallowing, saliva and speech.

The HRQoL is better in patients treated with laser excision or primary closure compared to free tissue transfer reconstruction.[63] However, the extent of tumour ablation and the need for reconstruction will depend on the stage of disease. Reconstruction of the tongue and floor of mouth using local methods can provide good function outcomes and shorten operating time, and surgical morbidity.[64] There are a variety of soft tissue free flaps for reconstruction and the choice of flap has relatively little influence on most HRQoL domains. There will be differences in donor site morbidity.[65] For example, with mandibular resection, the need for adjuvant radiotherapy is a more important influence on HRQoL rather than whether a segmental or rim resection is performed or a composite free flap is used.[66] The survival advantage needs to be balanced against increased treatment toxicity. Post-operative radiotherapy (PORT) can be associated with reduced global health status, increased xerostomia and marginally increased levels of fatigue at 6 months post treatment for oral cavity cancer.[67] Adjuvant radiotherapy has a significant effect on HRQoL mainly because of dry mouth.[68] The patients' ability to cope with oral cancer is remarkable; the HRQoL in people who survive more than 5 years, when assessed with the SF-36 questionnaire was similar to those of the general population, even exceeding these reference values in some dimensions.[69]

Maxilla

Debate continues around the importance of obturation or free tissue transfer on HRQoL for the maxillectomy defect.[70] Obturator prosthesis is a highly positive and non-invasive approach to improve the quality of life of patients with maxillectomy defects.

There is an element of patient preference, however, with the large complex resections (palate, maxilla, sinuses, orbital content) HRQoL outcome is arguably better with microvascular reconstuction.[71] It is likely that edentulous obturated patients have worse outcomes than dentate patients, and although the size of the maxillectomy defect might have relatively little bearing, adjuvant radiotherapy results in worse mouth opening and self-reported oral and swallowing problems.[72]

Oropharynx

The oropharynx site brings into focus the debate around organ 'preservation' (non-surgical treatments) and surgery combined often with radiotherapy.[73] The stage[74] and treatment[75, 76] are key determinants of HRQoL outcomes. There is some evidence that there is a tendency for improved HRQoL among patients with oropharyngeal carcinoma treated surgically compared to advanced stages of disease managed with primary chemoradiotherapy.[77] There has been considerable interest in HRQoL as treatment affects aspects of social function for the patients such as speech and swallowing. There have been different treatments advocated such as transoral laser surgery, transoral robotic surgery with risk stratified adjuvant radiation or chemoradiotherapy. With radiotherapy, there is a body of evidence developing in support of intensity-modulated radiotherapy (IMRT). The association with HPV has raised the possibility of treatment de-escalation with better HRQoL and equivalent survival. T stage, tumour involvement of the tongue base, professional status and emotional and social functions can be considered as the main determinants of HRQoL,[78] while HPV status itself is not a main determinant.[79] Early disease can be treated with high long-term HRQoL by surgery alone. Primary surgery with PORT in selected patients with limited primary tumours and advanced neck disease renders excellent HRQoL. IMRT is superior to former radiation techniques with regard to HRQoL, and should be considered as standard of care in patients undergoing RT for oropharyngeal squamous cell carcinoma (SCC).[79] Further efforts to reduce swallowing dysfunction are likely to yield additional gains in HRQoL.[80]

Larynx

The outcomes of patients with early stage glottic cancer report significantly better HRQoL and function specific patient-reported outcome measures (PROMs) than those with more advanced stage disease. When attempting to make comparison between voice handicap and QoL after radiotherapy versus endoscopic laser resection (ELR) for T1a-glottic carcinoma, results should be interpreted in light of the biases inherent in retrospective studies. There is little difference with T1-laryngeal disease treated with ELR and radiotherapy.[81] Laoufi et al.[82] concluded that long-term subjective voice-related quality of life was worse after ELR, with no difference in other domains and larger T2 tumours might have better speech outcome with primary radiotherapy. However, T2 tumours, in particular T2b, and continuing smoking after radiotherapy correlated significantly with poor local control and worse voice handicap index.[83]

Partial laryngectomy procedures such as vertical or horizontal partial laryngectomies, have a role in attempting to optimize function and hence HRQoL. Modified supracricoid laryngectomy seems to improve quality of voice and QoL in patients with early laryngeal cancer.[84] The HRQoL benefits for extended vertical hemilaryngectomy and reconstruction with a neovascularized tracheal autograft for advanced unilateral laryngeal tumours need further evaluation.[85]

TOTAL LARYNGECTOMY

Following laryngectomy, areas that tend not to recover to baseline level are physical functioning, role functioning, social functioning, fatigue, dyspnoea, appetite loss, financial difficulties, senses, speech and social contact. Rather than age, sex, education and tumour site predicting HRQoL outcome, it is tumour stage, recurrent disease, radiotherapy and mental health.[86] Patients can be more accepting of, and find less troublesome, anticipated sensory impairments, cough and dyspnoea, than more general side effects such as constipation and nausea/vomiting.[87] Despite common belief, many patients who have undergone total laryngectomy (TL) maintain a good overall QoL.[88] There are potential difficulties in returning to work after TL. Influencing factors include age < 50 years, being self-employed or a clerical employee, good physical functioning, good speech intelligibility, high motivation to go back to work, and support from colleagues.[89] There is evidence around the impact on HRQoL and primary and secondary tracheo-oesophageal puncture (TEP).[90] Primary TEP provides almost immediate and satisfactory voice rehabilitation. Chemoradiotherapy and patient age do not seem to affect voice quality with either procedure.[91]

Comparison between TL and concurrent chemoradiation for function and long-term QoL outcomes in pharyngolaryngeal carcinoma patients shows no significant difference concerning feeding-tube, oral supplements and respiratory related HRQoL items. Differences are encountered in aspects such as smell and taste (surgical) and with dry mouth and weight loss (with chemoradiation).[92]

Skull base

There is a relative lack of HRQoL outcome data related to skull-base cancer. The development of an Anterior Skull Base Surgery Questionnaire (ASBS-Q) has improved our understanding of the PROM following skull-base cancer.[93] The overall QoL of patients

following endoscopic extirpation of skull-base tumours is good. Endoscopic skull-base surgery is considered a minimally invasive surgical modality with less morbidity and patient discomfort. It appears that endoscopic approaches are not associated with a detrimental long-term effect on sinonasal-related QoL. Short-term impairments of sinonasal-related QoL are predictable and self-limited.[94] Comparison of the impact of the open and endoscopic skull-base surgery on HRQoL revealed that patients who have endoscopic surgery reported significantly better scores in the physical function and impact on emotion domains than the patients who have open subcranial surgery.[95]

STAGE

Stage of disease is consistently one of the main influencing factors for HRQoL outcomes.[5, 9] Stage is related to the extent of the cancer, radicality of treatment, and associated functional deficits. The clinically meaningful significant differences in HRQoL between early stage and late stage HNC is reflected in most papers on this subject. The implication of this finding is that promoting early cancer presentation would make a significant difference not only on survival (patients' first priority) but also HRQoL.

TREATMENT

In general, single modality treatment, radiotherapy or surgery alone, confers much better HRQoL.[96] Transoral robotic surgery might be a way of preserving functional anatomy without compromising surgical resection margins and could have a positive impact on HRQoL,[97, 98] The advantage of less invasive surgery on HRQoL (e.g. transoral resection versus open resection and free-flap reconstruction[63] or rim mandibulectomy versus segmental resection)[66] is lost if primary surgery has to be followed by adjuvant radiotherapy. Avoiding radiotherapy after primary surgery has substantial benefits for patients in terms of HRQoL as long as optimal survival is maintained.[68, 99] There is evidence that reducing the dosage of radiotherapy can make a substantial difference.[100] In addition, IMRT has much better HRQoL outcomes compared to 3D-conformal radiotherapy (3D-CRT).[101]

Outcomes for overall HRQoL are similar for surgery with reconstruction compared to radical radiotherapy,[102] and for radical surgery and radiotherapy compared to chemoradiotherapy. There are functional differences in these comparisons such as greater impairment of speech and shoulder function after surgery whereas after chemoradiation, patients suffer from greater pain, xerostomia, difficulty swallowing and problems chewing.[103] Although the short-term side effects of treatment may differ between the groups, long-term QoL is remarkably similar whether the patients choose primary chemoradiation or surgery with post-operative radiation.[104, 105] Global QoL scores might be associated with slightly better functional outcome with surgery, and from the perspective of functional outcomes, either surgery or chemoradiation seem appropriate treatments for advanced HNC[106] but better long-term HRQoL scores are seen in patients undergoing concurrent chemoradiation.[107] Osteoradionecrosis (ORN) of the mandible is a severe complication of radiation therapy and has a detrimental impact on HRQoL. Surgery for ORN can result in an improved HRQoL; however, lack of improvement, despite the restoration of an intact mandible, relates to the persistent effects of chemoradiotherapy.[108, 109]

Treatment intent

To date there is a relative paucity of information concerning HRQoL in patients treated with palliative intent and further clinical outcomes research is needed.[110, 111] The published studies have tended to be qualitative in design due in part to the absence of a suitable HRQoL questionnaire specific to palliative care in HNC.[112]

Clinical trials

In the literature the evidence base concerning HRQoL is limited in respect to clinical trials. HRQoL questionnaires are a component of a clinical trial often included as a secondary outcome, and not explicitly driven by hypothesis.[113, 114] In the future there will be an increasing number of trials and interventions specifically aimed at evaluating HRQoL differences such as a study to assess the effect of low-level laser therapy on PROMs of oral mucositis and QoL in HNC patients receiving chemoradiotherapy.[115] IMRT will continue to be the subject of trials' research for the foreseable future until it becomes a standard of care (see 'Xerostomia below').

HRQoL ISSUES

There is a diverse range of patient and carer needs and concerns after completion of HNC treatment.[106, 116, 117] The variety of HRQoL issues are reflected in **Table 20.3** and will be mentioned individually below. Issues include pain, skin reactions, mucositis, nutritional status, swallowing, voice and speech, hyposalivation and xerostomia, dental health, trismus, shoulder and tissue fibrosis, sleep, fatigue, anxiety and depression, body image and social isolation, taste and smell, cognitive function and work status. However, the most frequent issue that patients wish to talk about is fear of recurrence (FoR).[116, 118–124]

Carer support

The benefit of carer support is a key issue in terms of patients' HRQoL. The use of support services differs over time. During the treatment phase and in the early period following interventions, there is a need for a wide range of supportive care expertise, including dental hygienists, physical therapists, specialist dietician and speech

TABLE 20.3 The vast array of different aspects to HRQoL following HNC

Alphabetical list
Carer: positive carer support
Coping: social support seeking good, avoidance bad
Dental status: eating- social interaction-coping
Disfigurement: appearance, body image, intimacy
Emotion: anxiety pre-treatment, depression is treatable, mood
Fatigue: common in year 1, poor sleep, low energy
FoR: does not lessen over time
Financial / work: employment, benefits, retirement
Information: various amounts, in various ways, at various times
Nutrition: low weight, diet, PEG feeding
Oral rehabilitation: chewing / eating – expectations + trade-off
Pain: need for opiates, poor sleep, depression
Personality: optimism and HRQoL + survival, high neuroticism
Self-esteem: low self-esteem associated with poor QoL
Sociodemographic: children, social support, ethanol abuse,
Speech: laryngeal speech / isolation
Swallowing: presence of feeding tube most significant
Shoulder: shoulder discomfort and neck tightness – selective
Trismus: poor difficulty in mouth opening – diet/social/intimacy
Xerostomia: profound impact on social function, IMRT
Unknown: clinical art of the individual not a precise science

therapists; long-term supportive care is more focused on aspects such as dental hygiene, speech therapy and physical therapy. Patients pecieved HRQoL deficits will influence their need for supportive care services.[125] Increased social isolation may be a risk factor for poorer physical recovery from, or adjustment to, treatment-related side effects. Social support may be an important target for psychosocial interventions for patients who face challenging treatment side effects.[126] Patients might view themselves as not being a burden to their carers but there is evidence emerging as to the demanding role placed on carers and family.[127] Carers see the patients as they are 'day-to-day' and not just at the review clinic episode. They are often more able to identify needs than the patient themselves recognize.[128] There are potentially many unmet supportive care needs and changes to the needs before and after treatment.[129, 130] Family caregivers report significant stress and needs themselves,[131] and the need for more information and healthcare services support. There is merit in devloping a tool to identify carer needs and caregiving training programs.[132]

Coping

The types of coping strategies patients adopt are important in terms of HRQoL recovery and adaptation.[133–135] Negative coping strategies need to be avoided as they are associated with poorer psychological state (higher incidence of depression, anxiety or low mood) and a reduced HRQoL. Post-laryngectomy avoidant coping strategies (both cognitive and behavioural escape) were among the strongest predictors of poor HRQoL.[136] To enable patients to implement positive coping strategies such as fighting spirit, coping with emotions and benefit finding is important.[137] Coping is part of a complex psychological construct linking QoL, coping styles, optimism and anxiety and depression.[138] Self-efficacy is also shown to positively influence social distress. Formal or informal support for HNC patients on how to cope effectively with disease can increase their resilience and perhaps reduce their reliance on a support network.

Dental status

Chewing and eating are part of social interaction. The significance of dental function cannot be underestimated with patients reporting chewing and eating being one of the most common issues they wish to discuss in clinics irrespective of the site (larynx, oropharynx, oral) or stage (early, advanced) of cancer.[122] The value of oral rehabilitation is not just in chewing, but also in self-esteem and well-being.[139] Oral rehabilitation is discussed in detail below.

Deprivation

Deprivation influences the incidence and outcome of patients with HNC. The more deprived the background of the patient, the worse the HRQoL outcome.[140] The relationship between deprivational and HRQoL is complex and is influenced by social support, lifestyle, comorbidity and coping strategies.

Disfigurement

Disfigurement embraces concepts such as appearance, body image and intimacy. It can be associated with shame and stigma[141] and social and emotional distress.[142, 143] The issue of body image disturbance has been addressed in a review by Rhoten et al.[144] There is a need to screen for appearance problems so that suitable advice and interventions can be offered.[145]

Emotion

The emotional impact of being diagnosed and treated for cancer cannot be underestimated, and certainly not least in HNC.[146]

There is a range of emotional distress syndromes but the main two components are anxiety and depression.[147–149] Anxiety is highest pre-treatment compared to depression, whilst depressive symptoms peak at the end of treatment and persist into survivorship for a proportion of patients.[150–152] Poorer survival has been associated with anxiety, depression, and worse HRQoL.[153] It is possible to screen for anxiety and depression in routine clinics[154, 155] and then to access a variety of interventions.[156, 157]

Fatigue

Fatigue, poor sleep and low energy are well-recognized symptoms during and following treatment, particularly in the first year. Depression and fatigue symptoms correlate negatively with HRQoL.[158] Fatigue-related items are common to several head and neck questionnaires but recently a Modified Brief Fatigue Inventory has been developed to measure intensity and frequency of fatigue specifically in HNC patients.[159] Comorbidity, cancer stage and adjuvant radiotherapy were associated factors. The excess fatigue reported in the IMRT cohort may, at least in part, be attributed to the dose distribution to the posterior fossa, cerebellum and brainstem.[160] Post-treatment hypothyroidism or subclinical hyperthyroidism induced by levothyroxine is associated with alterations in the HRQoL, reduction in the muscle function of upper limbs, and higher degree of fatigue.[59] The benefit of exercise is still to be defined in HNC, whereas it might be of benefit in other cancer sites.[161]

Fear of recurrence

FoR following treatment is common and significantly influences HRQoL.[116, 162] FoR is a major patient concern but is infrequently discussed in outpatient settings and may cause significant detrimental effect on the patient's psychological well-being.[118] Some patients experience intermittent and consistent levels of significant FoR, which do not improve with time and it is difficult to predict those based on clinical characterists.[163] There is merit in screening as this can lead to both informal and formal interventions.[164, 165]

Finance

Financial, work, employment benefits and retirement are factors in HRQoL for this patient group. For some, the cancer can be a time of positive readjustment moving to a slightly earlier retirement that planned. However, for those employed and with financial commitments the treatment and aftermath of cancer can be a substantial cause for concern and stress. Return to work is influenced by the type of job with 'white collar workers' such as professional, managerial, or administrative more likely to return than 'blue collar workers' (BCWs) for example involved in skilled or unskilled manufacturing. Considerably more severe impairments were reported in the self-administered questionnaires for BCWs and a poorer HRQoL.[166] Singer et al.[167] report that only a few laryngectomees return to work and they stress that return to work is important for many patients. Patient consultations should consider possibilities to support vocational rehabilitation before offering to apply for retirement. Survivors who perceived greater negative consequences of their cancer and worse physical functioning took longer to return.[168] In a study by Rogers et al,[169] 57% had suffered financially since diagnosis and QoL had decreased in 53% as a result of the financial impact of the disease. This was most common in the unemployed (64%), and in those whose work was affected by cancer (83%). Two-thirds had applied for benefits after diagnosis. Patients with worse physical and emotional functioning experienced more notable financial burden, more difficult life circumstances in the past month, greater financial difficulty and loss of income due to their condition in the previous week, more dissatisfaction with how well they took care of their own financial needs and were more likely to have sought statutory benefits.[170]

Gastrostomy

Although gastrostomy tube and swallowing, nutrition and function are covered in other parts of this chapter, this deserves individual mention because of the significant association with HRQoL.[171, 172, 173] Clinical stage, tumour site, patient age and nutritional parameters are all associated with the gastrostomy tube placement.[173] Patients with gastrostomies reported multiple deficits in HRQoL and a much poorer QoL. The presence of a feeding tube interferes with family life, intimate relationships, social activities and hobbies, in additon to the practical considerations of local discomfort, leakage or blockage. Permanent gastrostomy is a suitable surrogate indicator for HRQoL outcome.

Information

Patient and their carers need differing amounts of information, delivered in various ways, and at various times. Anxiety and supportive care needs are paramount during the diagnostic phase of the cancer journey.[174, 175] Anxiety and unmet needs are highest in those patients who experience a delay in diagnosis, treatment commencement, poor information and lack of psychological support.[175] Information provision needs to be tailored and include material about illness, treatment, side effects, function, physical fitness, impact on functioning, duration of recovery time, impact on QoL, support groups, where to go for financial advice and the long-term effects of treatment on ability to work.[41, 176] The internet has an important role for patients in providing information and support about their cancer, although other sources are still very important especially in the elderly and those early school leavers.[177]

Intimacy

Problems with sexuality and intimacy in HNC are under reported and have a detrimental imapct on HRQoL. Around one-third of those willing to answer intimacy and sexuality questions report substantial problems with sexual interest and enjoyment, and one-quarter problems with intimacy. The problem is particularly common in the under 55-year old age group.[178] The issue is complex and involved concepts such as 'personal identity', 're-establishing social networks' and 'intimate relationships', and is related to patients' perceived changes to self-esteem and image.[179] There is scope for intervention and pscho-sexual counselling but the concern is difficult to identify in clinical practice as discussion of this tends to be taboo.[180]

Nutrition

Malnutrition is common among HNC patients and negatively impacts on survival and QoL.[181] Unintended weight loss of more than 10% seems to be the most reasonable definition of malnutrition. More than 10% weight loss during and directly after radiotherapy has a significant impact on social eating, social contact, and HRQoL.[182] Chemotherapy and low body mass index at diagnosis are strong predictors of malnutrition.[183] Individualized dietary counselling on nutritional status is beneficial, compared to no counselling or standard nutritional advice and makes a positive impact on HRQoL. The effects of oral nutritonal supplements and tube feeding seem inconsistent in the literature.[184] Nutritional advice is still necessary years after chemoradiation.[185] Novel ways to encourage appetite should be considered.[186.]

Oral rehabilitation

Oral rehabilitation is a basic consideration for all HNC patients due to the importance that chewing, teeth and oral function have on HRQoL and well-being.[121, 139] Oral function influences swallowing, appearance, chewing, trismus, drooling and food clearance.[187] Oral rehabilation improves masticatory efficiency and this impacts positively on both food choice and social life. Consumption of solid, semisolid and overcooked food can be considerably better with the prosthesis.[188] After rehabilitation there is less worry about maxillary prostheses falling out, less embarrassment while conversing, less worry about losing self-confidence from embarrassment caused by dentures and fewer drooling problems.[189] The positive treatment outcome of oral rehabilation is not always predictable as some local effects following soft-tissue resection or radiotherapy cannot be significantly improved by prosthetic rehabilitation leading to functional and emotional disability.[190]

Pain

Pain is a major factor that influences a patient's QoL in relation to HNC. It is a common item in most HRQoL questionnaires.[7] Pain levels relate to HRQoL, the need for opiates, poor sleep and depression.[191] Different questionnaires are used to measure the extent and intensity of pain; however, further research needs to be undertaken to create a better objective, validated pain-related questionnaires.[192] Screening for pain in clinic can allow for intervention and when necessary, onward referral to a specialist pain team.[193]

Personality

Personality, ways of coping, mood and distress all have a bearing upon HRQoL. High neuroticism, avoidance focused coping, drinking to cope and high alcohol consumption are associated with worse distress.[135, 194, 195] Moreover, personality types and coping choices can correlate to survival.[196] The link between HRQoL and coping means that clinicians should be aware of the various positive and negative coping strategies and enlist the help of a clinical or health psychologist.[197]

Self-esteem

Low levels of self-esteem are linked to poor HRQoL and are influenced by issues such as shame and stigma,[141] oral function,[139] intimacy,[179] disfigurement,[142] support needs and family.[132] There are significant differences in anxiety and depression between those patients who have high self-esteem compared to those with low self-esteem. Ideally, patients with low self-esteem need pre-treatment and ongoing intervention.[198] The evidence relating to psychosocial interventions is considered later in this chapter.[157]

Sociodemographics

In a study by Rodriguez et al,[199] the most important contributor of overall HRQoL for people recently diagnosed with advanced cancer was social support. It was followed by general health perceptions, energy, social function, psychological function and physical function. In another study, patients with more support reported less anxiety and depression and better HRQoL in the mental health domain, independent of demographic and medical variables.[200] The degree to which individuals have the capacity to obtain, process, and understand basic health information and services needed to make appropriate healthcare decisions (health literacy) is important. Beitler et al.[201] found that patients who underwent TL had a high chance of being lost to follow-up as well as having inadequate healthcare literacy. When assessing the impact of treatment in respect to HRQoL outcomes it is essential to consider the individual, his or her background and their context for the cancer and survivorship.

Shoulder

The morbidity associated with radical neck dissections and the impact of shoulder dysfunction and pain is well recognized.[202, 203] Where possible selective neck dissections should be performed as the function and HRQoL is much better.[204] There is little subjective morbidity associated with shoulder dysfunction after a unilateral 3 or 4 level neck dissection compared with patients undergoing primary surgery without a neck dissection.[205] Also following selective dissection, patients usually rate poor shoulder function of less importance than other items such as swallowing, speech, dry mouth, chewing and appearance.[206] If level IIb can be safely spared there is some evidence that the accessory nerve function is better.[207] Identifcation of a 'sentinel node' offers potentially the least morbid approach and early reports show HRQoL benefit, for example, less appearance dysfunction related to marginal mandibular nerve weakness and scarring.[208, 209]

Speech and voice

Speech is one of the main HRQoL issues following HNC[121] as it impacts on social function,[210] and contributes to isolation.[5] Radical treatment can have a significant impact on speech, voice and communication outcomes. The assessment is complex and lends itself to specific questionnaires.[211–215] Voice and speech impairment are prevalent;[216] for instance, over two-thirds of surviving oropharyngeal cancer patients will have speech impairment. The main clinical correlates associated with adverse patient and observer-rated speech and voice outcomes are tumour stage, combined treatment (surgery and radiotherapy) and free-flap reconstruction.[217] Local flaps (pharyngeal flap) can improve function and HRQoL in more than half soft-palate resections.[218] Following endoscopic resection or radiotherapy for early glottic cancer HRQoL and voice appear similar despite the two different treatments,[219] and based on functional outcome, patients can have a choice of treatment for early glottic cancer.[220] Voice restoration following TL is an important part of patients' rehabilitation and long-term QoL. Primary TEP provides almost immediate and satisfactory voice rehabilitation. However, it may not be ideal in all clinical scenarios and secondary TEP may be needed. Chemoradiotherapy and patient age do not affect voice quality with either procedure.[91] Voice-related quality of life (V-RQoL) outcomes for patients using tracheo-oesophageal speech had similar V-RQoL outcomes compared to oesophageal speech (ES), and both performed significantly better than electrolaryngeal speech (ELS). For ELS, the total V-RQoL score was better with longer time after surgery and older age.[221]

Swallowing

The importance of swallowing in HRQoL outcomes cannot be underestimated. In this chapter there is only space for a cursory summary of key concepts. The link between nutrition, social function and carers is important and there is the association of permanent gastrostomy with poor HRQoL.[171, 222] It is essential that patients and caregivers attend pre-treatment clinics to discuss nutritional support via the artificial route; their QoL can be enhanced if guided through a specialist support pathway based at the clinical site where they initiated their care, with links to key agencies.[223] Prophylactic gastrostomy insertion can be associated with significantly earlier start and longer use of enteral nutrition, fewer malnourished patients over time, and improved HRQoL at 6 months after start of treatment but there has to be a drive to assist the patient to achieve an adequate swallow to allow the feeding tube to be removed wherever possible.[224] Advanced T-stage, free-flap reconstruction, younger age and base of tongue tumours have a negative impact on post-treatment swallow function and related HRQoL in these patients.[100, 225–228] Swallowing dysfunction following chemoradiation is a major cause of morbidity and reduced HRQoL related to early and late toxicity.[229] More clinical outcomes research is a priority in this area through prospective and randomized studies, robust cohort studies comparing types of feeding and treatment, and interventions.[230, 231] Screening in clinic allows the opportunity for patients and carer support.[232] For more detailed assessment, questionnaires should be accompanied by objective measures and there can be differences between the two evaluations.[232] Long-term dysphagia is influenced by mean radiation doses to the constrictor muscles and there is potential advantage in reducing the RT dose to swallowing structures to avoid severe dysphagia.[233–235]

Taste

Alteration of taste (dysgeusia) is a relatively common complication of head and neck radiotherapy and has a detrimental effect on HRQoL.[236, 237] Taste alteration can influence patients' enjoyment and choice of foods[238] and their dietary energy intake.[239] Consumption of sugary foods (cariogenic) places dentate patients at risk of radiation related caries.[240]

Trismus

Trismus (limited mouth opening) is a common symptom and the incidence is in the region of one-tenth at presentation, one-third at 6 months and one-quarter at 1 year after treatment.[241] The incidence can be higher depending on the criteria used to define trismus.[242, 243] Trismus severely impairs HRQoL through issues such as pain, eating, chewing, taste, saliva, social functioning, social contact and dry mouth.[241–243] Structured exercise with jaw mobilizing devices can improve mouth opening on trismus and have a positive effect on trismus symptomatology and HRQoL.[244]

Xerostomia

As previously mentioned, the severity of of xerostomia correlates with oral discomfort, difficulty chewing/swallowing/speaking, altered taste and low mood.[245] Sticky saliva and profund dryness at night can be major issues.[246] Prevention is better than measures aimed at symptom control; hence there have been technological advances in the delivery of radiotherapy and this has led to less salivary gland hypofunction with sparing of the partoid glands and a potential improvement in HRQoL.[247, 248] IMRT is a technique that allows delivery of lower doses of radiation to normal tissue, while maintaining or increasing the tumour dose, compared with two-dimensional radiotherapy (2DRT) or 3D-CRT. Patients treated with IMRT experience statistically significant improvements in several important HRQoL domains.[249] IMRT had significantly better outcome in various scales such as global QoL, physical functioning, swallowing, senses (taste/smell), speech, social eating, social contact, teeth, opening mouth, dry mouth, sticky saliva and feeling ill.[101, 250] Adaptive head and neck radiotherapy (ART) is a new concept in which there is dose avoidance to anatomical structures. A timed

replan can achieve dosimetric improvement and needs further outcomes research.[251]

Unknown

In spite of the many issues impacting on HRQoL reflected in this chapter, there is still a lot we do not know. HRQoL is a clinical art of the individual and not a precise science. The patient response is not all negative and it is possible, from their experience, to get a different perspective and have a profound influence on the person's QoL.[252] Survivors benefited from support and understanding offered by family, friends and healthcare professionals. This difficult situation can serve as a catalyst for deeper human change. In spite of the major changes such as following laryngectomy, the support of family, friends and healthcare professionals can encourage a successful transition to recovery.[253]

HRQoL IN FOLLOW-UP

Routine assessment

It is very important to adopt a holistic approach to patients' care throughout their follow-up. Patients can report distress at differing time points. Distress negatively impacts on HRQoL.[254] HRQoL screening may permit early identification of problems that influence HRQoL outcomes and may also facilitate timely intervention.[255] HRQoL questionnaires are limited for holistic assessment in routine clinic.[193] Consequently, some of the patients' concerns will be under-recognized and this will lead to unmet needs, poor communication, delayed recovery, further distress and dissatisfaction. The Patient Concerns Inventory (PCI) has been developed to help patients raise issues in their consultation that would otherwise be missed and also to request the opportunity to see or be referred on to other members of the MDT.[256] Despite the PCI comprising of 57 items, it has been shown not to delay the consultation, as there is evidence that both the clinician and the patient focus on what they wish to say in the consultation more efficiently.[257, 258] As an indicator of quality of care and helping to reflect the patients' experiences, the PCI has been included in the national HNC mandatory audit (DAHNO).[259] Advances in information technology and patients' familiarity with computers and the internet will in the future allow for a much more integrated approach to HRQoL assessment and intervention.[260, 261]

Interventions

As our understanding of the HRQoL outcomes of patients has increased in recent decades this has led to a focus on intervention. There are many different interventions reflecting the scope of HRQoL in the post-treatment patient. Semple et al.[157] published a review of psychosocial interventions. Evidence for interventions is limited by the small number of studies, methodological problems and poor comparability. Future interventions should target HNC patients who screen positive for clinical distress and be integrated into standard care.[156] Certain groups of patients might be more suitable for targeted interventions, such as those having chemoradiotherapy, where the HRQoL outcomes are worse.[262] A nurse-led intervention around the time of discharge from hospital, based on informational needs, has potential benefits to HRQoL and satisfaction.[263] Early provision of psychotherapy might reduce post-traumatic stress disorder, anxiety and depressive symptoms, and prevent chronic psychopathology.[264] Interviewing patients to allow them to express their concerns has merit.[265] In the work stemming from the PCI, FoR has been found to be the commonest concern that patients wish to talk about at outpatient consultations.[118] The AFTER (Adjustment to the Fear, Threat or Expectation of Recurrence) intervention has been developed [266, 267] and needs further evaluation. Acupuncture as an intervention has been evaluated. It has been used in the prevention and treatment for radiation-induced xerostomia.[268] When given concurrently with radiotherapy and compared with sham acupuncture it significantly reduced xerostomia symptoms and improved HRQoL.[269] In a randomized crossover study by Simcock et al.[270] eight sessions of weekly group acupuncture compared to group oral care education showed significantly better relief of symptoms in patients suffering from chronic radiation-induced xerostomia. Holistic alternative approaches have also been investigated; examples include intra-oral low-level laser therapy for patients receiving radiotherapy and complementary and integrated therapies (CIT) such as relaxation massage.[271, 272] There is scope for other interventions such as for secondary lymphoedema to help in the management of associated symptom burden, functional loss and psychosocial impact.[273]

Lifestyle

There is a risk associated with continued smoking and alcohol consumption after diagnosis and this affects survival outcomes.[274, 275] Patients with HNC are at considerable risk for other chronic conditions, such as coronary heart disease, causing around one-quarter of deaths. Also, secondary cancers are prevalent.[276] Comorbidity impacts on survival[277, 278] and HRQoL,[279–281] hence it is important to include staging and outcome analysis.[282]

CONCLUSION

HRQoL is now an integral part of the management of the head and neck patients and their carers. In the future, it is likely that enhancements in information technology will allow HRQoL to be routinely integrated into the patient pathway. Also, as our understanding of the patients' perspective of outcome increases, so treatment selection will become more refined and aftercare determined by the needs of the patient.

KEY POINTS

- HRQoL is an essential component when reporting outcomes following head and neck cancer.
- HRQoL is usually measured by questionnaires. The choice of questionnaire is an important consideration and depends on the reason for collecting the patient reported outcomes.
- Many factors impact on HRQoL and relate to the physical/functional, social and emotional consequences of treatments.
- HRQoL questionnaires can be augmented by using prompt lists such as the Patients Concerns Inventory in order to give a more holistic approach to clinical care.
- Advances in computer technology will make a substantial difference in helping to collect HRQoL outcomes and allow this to be use on an individual patient basis for interventions.

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CHAPTER 21

PALLIATIVE CARE FOR HEAD AND NECK CANCER

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SEARCH STRATEGY

Data in this chapter may be updated by a Medline search using the following keywords: palliative and end-of-life care.

THE ROLE AND CHALLENGES IN PROVIDING PALLIATIVE CARE TO HEAD AND NECK CANCER PATIENTS

Head and neck cancer accounts for around 8000 cases per year in England and Wales and up to half of all these patients will die from their illness and will require palliative support.[1] The World Health Organisation (WHO) defines palliative care as being the 'total active care of patients whose disease is not responsive to curative treatment'.[2] The fundamental principle of palliative care is that it should 'offer a support system to help patients live as actively as possible until death and....help the family cope during the patient's illness and in their own bereavement'.[3] The care should be both patient-focused and family-centred and encompass physical, psychological, social and spiritual aspects of care.

With this holistic approach to care and treatment, the overall goal is the achievement of the best quality of life for patients and their families, a parameter recognized to be as important to patients as actual survival and avoidance of recurrence.[4, 5] Patients with head and neck cancer represent a complex group, in part related to the unique properties of the disease itself and the impact the illness and treatments have on different organ systems essential for human functioning e.g. communication, swallowing and breathing.[1, 4] The resulting functional deficit and symptoms that arise can be challenging to treat[6] and can have an impact on the patients' psychological well-being due to resulting social isolation and depression.[4] Additionally, the focus and type of treatment can contribute to the care challenges; those who undergo potentially curative surgery for advanced or recurrent cancer can still have significant morbidity and a limited prognosis and may be considered by some to be palliative.[7] The concept surrounding the terms 'radical' and 'palliative' treatment are challenged when caring for head and neck cancer patients.[8] An ideal palliative treatment is defined as one which provides symptom relief without producing significant morbidity; radiotherapy doses given to induce tumour regression and relieve symptoms are in the range used for cure and can cause painful mucositis and xerostomia; surgical intervention can be accompanied by disfigurement and functional loss.[8] The diagnostic difficulties raise a further challenge; sometimes, due to previous treatments, it can be difficult to obtain histological confirmation of disease recurrence causing uncertainty regarding appropriate referral for palliative care input.

Since the inception of the modern hospice movement by Cicely Saunders in the 1960s, palliative care has expanded.[9] Specialist palliative care units (or hospices) traditionally operated outside the National Health Service (NHS) and were funded by voluntary donations. Since the 1980s however, this situation has been changing with many hospices entering into financial partnerships with the NHS. Palliative Medicine became a recognized speciality in the UK since 1987[10] and increasing numbers of multidisciplinary palliative care support teams have been established within hospitals and the community. Multidisciplinary teams (MDTs) both within hospices and as advisory teams are an integral and key part of specialist

palliative care services and aim to bring together different healthcare professionals with the knowledge and expertise to ensure the appropriate treatment and care is given to each individual patient.[2]

Generally, when assessing the need for palliative care input and support, the decision for referral should be based on need rather than diagnosis, although clear explanations to both the patient and palliative care colleagues may be required regarding roles and responsibilities. Within the last decade, there has been recognition of the need to move palliative care 'upstream' in the disease trajectory and integrate more with curative and rehabilitative therapies rather than the more traditional involvement immediately prior to death (**Figure 21.1**).[9, 11]

Timon and Reilly[13] estimate that approximately 20% of head and neck cancer patients would qualify for palliative care input at the time of initial diagnosis, with an average survival of 5 months within this cohort. Shuman et al[11] suggest the following situations for review regarding the need for palliative care:

- unresectable locoregional disease and/or distant metastasis at initial presentation
- patients with recurrent unresectable locoregional disease and/or distant metastasis after treatment
- patients unable to have anticancer treatments due to disease stage, comorbidity, functional status and/or individual preference.

While this is a useful principle, it may not always be as clear-cut in practice as symptom burden or needs may indicate that palliative care involvement would be beneficial. Many principles of palliative care management are applicable earlier in the course of the illness, often in conjunction with anticancer treatment.[8] Generally, improved patient outcomes can be achieved by a proactive approach with the involvement of palliative care colleagues for advice about symptom control, joint discussion and decision-making and advanced care planning. There is a lack of data, evidence and outcomes regarding the needs and management of end-of-life for patients with head and neck cancer.[6] Further research is needed in this area to guide patient management and improved outcomes.

COMMON PALLIATIVE PROBLEMS IN HEAD AND NECK CANCER

Common symptoms that arise with head and neck cancer patients include pain, dysphagia, fatigue, weight loss and breathing difficulties[6, 14] although many other symptoms and concerns can arise (**Table 21.1**). A retrospective review of 93 terminal head and neck cancer patients showed that patients had a mean number of 4.7 (+/– 2.67) symptoms in the last 6 months of life.[14]

Within this section, an overview will be provided of the following issues: pain, respiratory tract secretion management, communication difficulties, and emergencies including terminal haemorrhage and airway obstruction. For more specific details about other symptoms and specific medications, reference to specialist palliative care textbooks such as the *Oxford Textbook of Palliative Medicine*[18] and the *Palliative Care Formulary*[19] is advised.

Pain

In head and neck cancer patients, pain is a common symptom with studies estimating the prevalence to be between 62% and 99% (**Table 21.1**). Pain can be sub-divided into two main categories:

- Nociceptive pain: arising due to ongoing activation of primary afferent nerves by noxious stimuli (nociceptors)[20]
- Neuropathic pain: due to dysfunction or disease affecting the peripheral and/or central nervous system.[21]

Within clinical practice, there can often be a mixture of both nociceptive and neuropathic pain which can arise either due to the cancer itself (local compression or invasion) or related to previous treatments.

The principles of effective pain management are governed using the WHO pain ladder which remains a useful, practical approach to managing cancer pain (**Figure 21.2**).[22] This step-wise approach advocates the use of non-opioids first-line (e.g. regular paracetamol); then the addition of a weak opioid such as codeine; then proceeding on to substitute the weak opioid for a strong opioid. Generally, the opioid of choice for moderate to severe pain remains morphine.[24]

The concept and understanding of opioid-induced neurotoxicity has become increasingly recognized due to accumulation of opioid metabolites.[25] Clinically, the patient will present with symptoms such as myoclonus, peripheral shadows, hallucinations, confusion and drowsiness. In this situation, the following should be considered:

- Can the current dose of the opioid be reduced (if pain is controlled)?

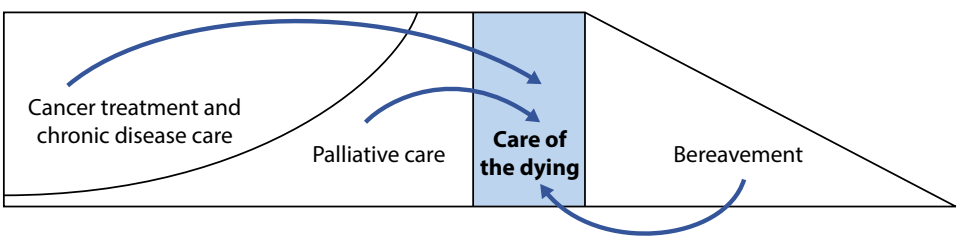

Figure 21.1 Involvement of palliative care within disease trajectory.[12]

TABLE 21.1. Symptom prevalence in advanced head and neck cancer

Author	Talmi et al.[15]	Price et al.[14]	Ethunandan et al.[16]	Ying-Li et al.[17]	Forbes[8]
Year	1995	2009	2005	2011	1996
Setting	Hospice, Israel	Mayo Clinic, USA	Hospital, hospice, home, nursing home, UK	Palliative care unit (PCU) within hospital, Taiwan	Hospice, UK
Method	Last hospice admission before death	Review of clinic notes in 6 months prior to death	Review of case notes for last week of life	Review of charts on admission to PCU	Last hospice admission before death
Patient numbers	67	93	32	94	38
N (%) with symptoms					
Pain	66 (99) 52 (77%) had severe pain	58 (62)	27 (84)	91 (97)	30 (79)
Dysphagia	Not reported	42 (45)	20 (63)	85 (90)	28 (74)
Fatigue/weakness	Not reported	36 (39)	Not reported	Not reported	Not reported
Weight loss/anorexia	63 (94)	40 (43)	Not reported	92 (98)	30 (79)
Breathing/airway difficulties	15 (22)	48 (52)	Not reported	41 (44)	11 (35)**
Feeding difficulties	22 (32)	Not reported	Not reported	84 (89)	28 (74)
Bleeding	6 (9)	13 (14)*	5 (16)	30 (32)	18 (47)

* This includes bleeding from tumour; haemoptysis; mucosal bleeding and bleeding from stoma.
** Problems with secretions.

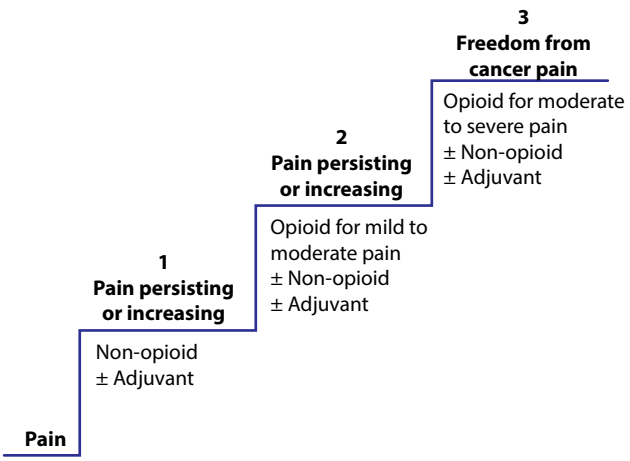

Figure 21.2 WHO pain relief ladder[23]

- Is the patient's renal function stable (as metabolites are more likely to accumulate if opioid is renally excreted)?
- Does the patient require an opioid switch?

In the latter situation, the current opioid medication should be switched to an alternative such as morphine to oxycodone or hydromorphone. If there is evidence of renal impairment, using opioids which are not excreted by the kidneys is beneficial e.g. alfentanil.[26]

In terms of addressing neuropathic pain, in addition to using the WHO ladder, the first-line approach to treatment is either using an anti-convulsant (e.g. gabapentin) or anti-depressant (amitryptiline) medication. If there is evidence of nerve compression, a trial of corticosteroids (dexamethasone) could be considered. Other therapeutic interventions would include the use of methadone, ketamine and potentially interventional pain procedures, and the involvement with specialist palliative care teams would be beneficial for this advice.

There have been more recent developments in the concept of 'breakthrough pain'. The Association of Palliative Medicine within the UK defines this as 'a transient exacerbation of pain that occurs either spontaneously, or in relation to a specific predictable or unpredictable trigger, despite relatively stable and adequately controlled background pain'.[27] Usually, in this situation a short-acting preparation of morphine is given e.g. oramorph or oxynorm. There are newer formulations of strong opioids (fentanyl) which can be administered via sublingual, buccal and intranasal routes, for this type of pain. They have been shown to have equal efficacy compared with traditional oral medications,[28] quicker onset of action but are more expensive. In practice, they tend to be reserved for pain related to a particular event e.g. movement or pain that is sudden in onset and short-lived. It is noteworthy that prior to use, patients should be on at least 60mg of oral morphine or the equivalent.

Particular challenges that arise for patients with head and neck cancer include the route of administration as often the oral route cannot be used. Where a gastrostomy tube is in place, medications can be given this way. It is particularly noteworthy, however, that sustained release preparations of opioids should not be crushed or opened when administered via this route. There are modified-release granules (Zomorph) and suspension (MST Continus) that can be used safely.

The transdermal method of delivery remains an alternative way of delivering opioid medication e.g. fentanyl

patch but it is important to be mindful of the following key messages related to their use:

- transdermal patches should only be used when pain control has been established and is generally stable
- transdermal patches tend to be changed every 72 hours so they do not have as much flexibility in terms of dose titration
- some forms of the buprenorphine patch (e.g. BuTrans) have a maximum dose range (up to 20 mcg which is equivalent to just under 50 mg oral morphine.[29]

The administration of subcutaneous medication given via a continuous infusion (CSCI) is often associated with care of a dying patient. They can be used, however, earlier in the disease trajectory for head and neck patients and this would include as a temporary measure until a gastrostomy is inserted.

Respiratory tract secretion management

When considering the use of anti-secretory medications, the three main drugs are glycopyrronium, hyoscine hydrobromide and hysocine butylbromide. Comparison of these drugs has mainly been undertaken in studies looking at their efficacy in managing retained respiratory tract secretions associated with the last days of life. There is a lack of conclusive evidence about comparable efficacy, although due to the reduced likelihood of agitation and sedation, glycopyrronium may be preferred.[30] The balance needs to be reached between trying to reduce the amount of secretions and not making them too tenacious. If the oral route is not available and a gastrostomy (or equivalent) is not in place, transdermal hyoscine hydrobromide (Scopoderm) patches could be considered.

Communication difficulties

For patients with head and neck cancer, as the disease progresses, there can be increasing difficulties with speech. Alternative methods to aid communication can be using devices for artificially generated speech or using written communication, but the loss of the subtleties of communication can have a profound psychological effect on patients.[8]

Generally, it can be challenging to discuss the complexities of care and decision-making at any time, but with the additional impact of head and neck cancer on communication, this is even more heightened. It also highlights that advance care planning is even more pertinent for these patients while they are able to do so. Having open-ended discussions about the goals of care, potential future complications and issues and being proactive in screening for unmet information needs is an important principle to adopt within the management of these patients.[8]

Terminal haemorrhage

Care for head and neck cancer patients is especially challenging in the terminal phase of illness (the last weeks and days of life) due to the perceived risk of acute catastrophic events such as having a terminal haemorrhage[1, 11] or 'carotid blow out'. The actual occurrence of a terminal haemorrhage (defined as 'bleeding from an artery which is likely to result in death within a period of time that may be as short as minutes')[31] is low with rupture of the carotid artery system occurring in an estimated 3–5% of patients who have undergone major head and neck resections.[32] However, the anxiety and distress associated with the risk of this potential event should not be underestimated. With the increasing numbers of patients who wish to be able to die in their own home, there is the potential for terminal haemorrhage to occur in this setting.[33] Although it is important to be able to prepare the patient and family for this possibility, the benefit and burdens of such discussion need to be carefully balanced in order to avoid unnecessarily escalating distress about an event that may not occur.[33]

Certain factors can increase the risk of a terminal haemorrhage occurring including:

- tumour-related factors – proximity to carotid artery
- treatment-related factors – previous radical neck dissection and radiotherapy; post-operative healing problems
- systematic factors – coagulopathy; age >50 years; 10–15% loss of body-weight; and comorbidities e.g. diabetes mellitus.[33]

Sometimes there can be a herald or warning bleed which precedes the life-threatening haemorrhage or evidence of a ballooning or visible pulsation of arterial vasculature.[34] Trying to minimize the risk of terminal haemorrhage occurring is important. This includes reviewing the patient's current medication to ensure that anti-coagulants (warfarin, heparin) are stopped and other medications which effect platelet function or the coagulation pathway are reviewed and potentially discontinued e.g. non-steroidal anti-inflammatory medications, aspirin, selective serotonin reuptake inhibitor (SSRI) anti-depressants. In several cases arterial embolization by interventional radiologists following a sentinel bleed can delay a bleed or abrogate an ongoing bleed.

Ubogagu and Harris[33] published guidelines about the management of terminal haemorrhage. Although these were specifically for patients at risk of a terminal haemorrhage in their own home, the principles apply for other settings. The key principles include:

- somebody should stay with the patient (and family if present) to help reduce the anxiety and distress associated with the event
- dark towels should be used to reduce the visibility of blood
- an anxiolytic should be given e.g. 10 mg of midazolam given via deep intra-muscular injection due to its rapid onset and short duration of action.

The midazolam should be pre-emptively prescribed, although often in view of the rapidity of the event it is not needed, and certainly is secondary to the need to stay

with the patient. The aim of giving the midazolam is to reduce the patient's awareness and hence distress of the event. Additionally, it provides retrograde amnesia so that if the patient did recover, they would not have recollection of the event. Opioids are generally not needed in this situation unless the haemorrhage is not terminal and the patient is reporting pain. Providing sufficient support to both the family and the healthcare professionals involved is a key factor after the event.

Management at home is more challenging and ideally needs to include a full MDT discussion so that the community healthcare professionals are involved in care planning, the ambulance service are prepared (as they may provide acute support during immediate distress of the event) as well as having appropriate discussions with the patient and family.

Airway obstruction

A further complication that can lead to an acute catastrophic event is airway obstruction. Compromise of the airway can arise due to retention of secretions or by tumour encroachment into the airway or tracheostomy. Preparation for the patient, family and healthcare professionals that this event could occur is of key importance[11] although again the likelihood is thought to be rare. Decision-making about the appropriate level of escalation of treatment in the event of an acute airway obstruction is pertinent. Palliative surgical options include tracheostomy or debulking of the tumour within the airway if deemed appropriate.[35] In the palliative situation, pre-emptive prescription of an anxiolytic, such as midazolam, is appropriate for a terminal event. If there is clinical evidence of stridor, high dose (8 to 16 mg) dexamethasone[36] given via subcutaneous injection may be beneficial.

HOLISTIC CARE FOR THE HEAD AND NECK CANCER PATIENT

Spiritual issues

Spirituality can be interpreted as how an individual finds meaning, purpose and value in their life.[37] Although this meaning may be found within a religious context, it can also relate to achieving life goals, being at peace with oneself[38] or finding particular aspects of life worthwhile.[37]

As a routine part of the palliative care consultation, issues relating to this should be explored. For example, asking questions such as 'how are you coping?'; 'what gives you hope and strength?'; and 'do you ever question "why" this illness has happened to you?' This will enable a patient to share key concerns and the healthcare professional to explore the patient's priorities and wishes for their future care.

Depression

Depression is common in head and neck cancer patients, and as it can independently predict poorer quality of life, requires prompt diagnosis and treatment.[39] Additionally, head and neck cancer patients are noted to have a disproportionately higher suicide risk compared with the cancer population as a whole.[40] Part of this may be due to the higher prevalence of head and neck cancer among male patients and the association with tobacco and alcohol consumption, all of which have been associated with depression and suicide. Additionally, these patients may have more limited social support networks, impacting on their ability to cope.[11]

Brief screening measures can be useful for identification of depression in particular asking about anhedonia (loss of interest or pleasure in doing things) and low mood[41] as many of the traditional physical symptoms associated with depression occur commonly with advanced cancer e.g. weight loss, fatigue, reduced appetite. Treatment with both psychotherapy and anti-depressant medications should be discussed with patients and medication commenced where appropriate. Generally, SSRIs are often considered first line compared with tricyclic anti-depressants due to the latter often being poorly tolerated.[42] It is noteworthy, however, that SSRIs do have the potential to increase the risk of bleeding from the gastrointestinal tract which is a particular consideration for head and neck cancer patients. Mirtazepine is a noradrenergic and specific selective serotoninergic anti-depressant and may be associated with weight gain and sedation. Both of these may be acceptable side effects for cancer patients, particularly if the medication is taken at night.

Ethical issues

The four general principles of ethical decision-making include:[43]

- respect for autonomy – the individual's right to decide what is best for them
- beneficence – duty to act in a way that provides benefit
- non-maleficence – duty to act in a way that does not cause harm
- justice – the fair use and distribution of resources.

These principles form a useful framework to guide decision-making and care planning. Key to good practice is ensuring patient-centred decisions are made and providing explanations about the burdens and benefits of treatments to the patient. Particular ethical issues that arise for head and neck cancer patients include decisions relating to the provision of nutrition and hydration, especially those approaching end of life. Healthcare professionals should consider the individual values and wishes of patients and their families when undertaking decision-making. In view of the likely communication difficulties already highlighted, forward planning and discussions about these issues is pertinent to patient-centred care. Advanced care planning is defined as a 'process of discussion between an individual, their care provider, and often those close to them about future care' and most patients welcome the opportunity to have these types of discussions.[44] Ideally, these should be serial discussions, over a period of time and at intervals when the patient's

condition is relatively stable. Detailed evidenced-based national guidelines have been published within the UK.[45]

The General Medical Council (GMC) within the UK provides specific guidance about decision-making about hydration and nutrition by focusing on both patients 'approaching the end of life' (defined as those likely to die within the next 12 months), and those for which death is thought to be imminent and expected within a few hours or days.[46] A Cochrane review of clinically assisted hydration (CAH) (defined as providing fluids via the intravenous or subcutaneous route) in palliative care was unable to provide any firm recommendations about the use of CAH in dying patients due to the lack of good quality studies.[47] There is limited evidence that CAH may improve sedation and myoclonus,[48] but no evidence to suggest it will improve thirst, delirium or fatigue. Again, although the evidence is limited, CAH may exacerbate symptoms caused by fluid retention e.g. peripheral oedema and ascites. Overall, the review concluded that clinical decisions regarding CAH in the care of dying patients needed to be directed by the perceived benefits and harms on an individualized basis. Additionally, although CAH is regarded in law as a medical treatment,[49] many patients and families consider CAH to be a principle of basic care. This potentially creates tension and a point of ethical contention when making a decision to engage, withhold or withdraw fluids.

In practical terms, patients with advanced head and neck cancer often have a gastrostomy inserted as part of their earlier treatment and, if appropriate, this can be used as a route for hydration and nutrition. If the patient's overall condition deteriorates, the volume of fluid and feeds should be reviewed. For patients who are actively dying (i.e. in the last hours or days of life), often the desire for food or fluid reduces and is seen as a part of the dying process.[44] For those able to take sips of fluid, this should be continued and for all patients good oral hygiene promoted, appreciating that access may be more limited if there is local malignant disease. For most patients, CAH or nutrition is not required at this stage of their illness but a discussion with the patient (if able) and family members is often required to explain that they are dying from their illness rather than from a lack of hydration or nutrition. If concern is raised about this decision, the subcutaneous route can be used to provide fluids and is less burdensome compared with the intravenous route. It is not without complications, however, and these include local site reactions (pooling of fluid or cellulitus) and potentially more systemic problems with symptoms of fluid retention including retained respiratory tract secretions. If a decision is made to commence fluids in this way, regular daily review of the burdens and benefits of the treatment should be considered.

CARE OF THE DYING FOR HEAD AND NECK CANCER PATIENTS

Prognostication i.e. predicting when death will occur remains extremely difficult, with doctors often tending to overestimate prognosis in those with an incurable illness.[50] The recognition and documentation of particular disease trajectories has aided this process e.g. cancer tends to have a comparatively predictable trajectory with a steady decline and a recognized terminal phase (**Figure 21.3**).[48] Patients with head and neck cancer challenge this trajectory to an extent, however, as there is the risk of different modes of death occurring, e.g. acute complications such as terminal haemorrhage or from comorbidities such as chronic obstructive pulmonary disease (COPD).

End-of-life care policies for a number of countries focus on trying to enable more people to die in their preferred place of care which generally is at home.[51, 52] The majority of patients, however, continue to die within the acute hospital setting [53–55] and it is likely that patients with head and neck cancer are no exception to this trend. The provision of palliative care within the acute hospital sector, however, is not without its shortcomings. A recent national survey

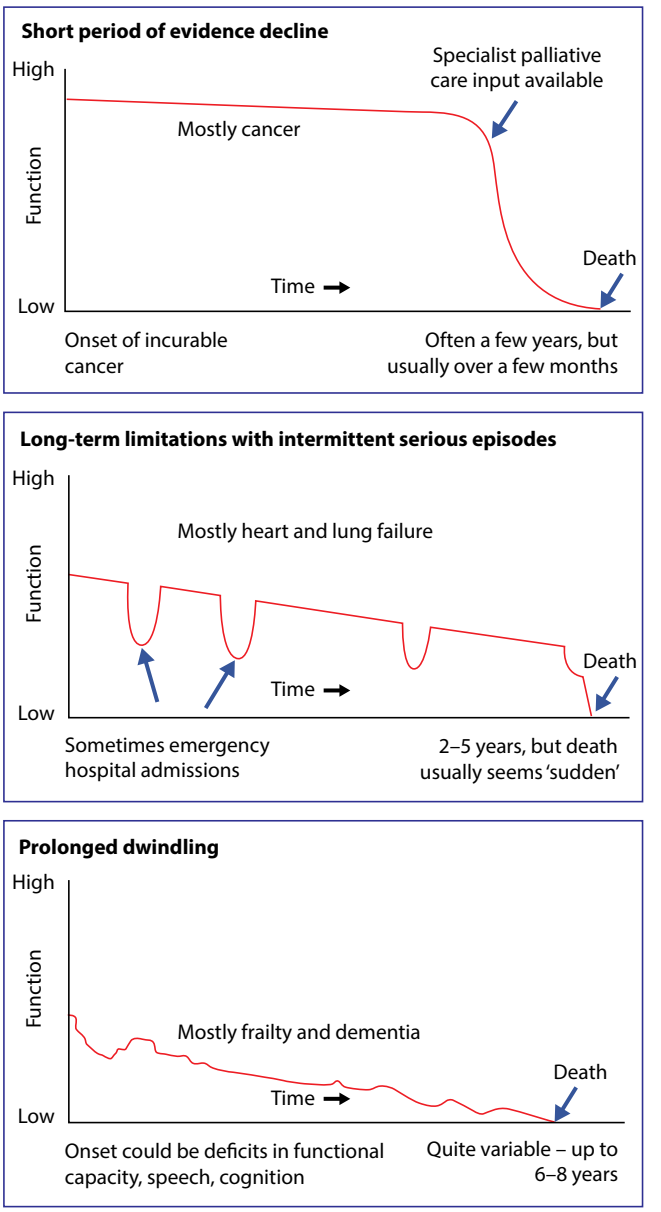

Figure 21.3 Typical illness trajectories for people with progressive chronic illness.[47]

BOX 21.1 The Priorities for Care are that, when it is thought that a person may die within the next few days or hours[58]

1. This possibility is recognized and communicated clearly, decisions made and actions taken in accordance with the person's needs and wishes, and these are regularly reviewed and decisions revised accordingly.
2. Sensitive communication takes place between staff and the dying person, and those identified as important to them.
3. The dying person, and those identified as important to them, are involved in decisions about treatment and care to the extent that the dying person wants.
4. The needs of families and others identified as important to the dying person are actively explored, respected and met as far as possible.
5. An individual plan of care, which includes food and drink, symptom control and psychological, social and spiritual support, is agreed, co-ordinated and delivered with compassion.

of bereaved people in the UK perceived that the quality of care for dying patients was not as high as the level provided at home, within the hospice or care home setting.[56] Recommendations have included increasing accessibility to specialist palliative care teams and mandatory training about care for dying patients for all healthcare professionals.[56] The most recent National report for 'End of Life Care Audit – Dying in Hospital' based on data collected in 2015, however, demonstrated that there were improvements compared with a similar audit undertaken in 2013: a higher proportion of patients were appropriately recognized to be dying in a timely manner and for 95% of these, there was a documented discussion about this recognition with those individuals identified as important to the patient.[57]

In terms of national guidance within the UK about the principles of providing care for those who are dying, the 'One chance to get it right' report identified five 'priorities for care'.[58]

'Individualized end-of-life care plans' are recommended and the subsequent publication of the NICE guidelines for end-of-life care has helped provide a framework for best clinical practice.[59]

Issues specifically related to care of head and neck cancer patients who are actively dying include the provision of adequate pain control. It is not generally recommended that transdermal fentanyl patches are commenced at this stage due to difficulty with titration. If the patient is already established on this method of analgesia, however, it should be continued and in the first instance, as needed injections of opioid used to help control pain. Depending on the amount of extra opioid needed, a continuous subcutaneous infusion (CSCI) should then be commenced in addition to the fentanyl patch.[60]

CONCLUSION

Caring for patients with advanced head and neck cancer is a complex area which raises unique challenges compared with other malignant diseases. Close collaborative working between head and neck cancer teams and specialist palliative care teams is important in addressing patients' needs and achieving high quality of care for the patient and their family. A pro-active approach to management of physical and psycho-social symptoms is needed to best meet patients' changing needs and providing best supportive care.

KEY POINTS

- Head and neck cancer patients have especially complex needs due to the impact the illness and treatment have on communication, swallowing, and breathing.
- Patients often have multiple symptoms including pain, fatigue, retained respiratory tract secretions as well as psychological distress causing depression.
- Advance care planning is important due to the potentially different modes of deterioration and subsequent death from this illness.
- Individualized care plans, incorporating a holistic assessment of needs, should support those who are actively dying.

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CHAPTER 22

TRANSORAL LASER MICROSURGERY

Mark Sayles, Stephanie L. Koonce, Michael L. Hinni and David G. Grant

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SEARCH STRATEGY

The initial search strategy involved PubMed, EMBASE, and Google Scholar database enquiries using the search term *transoral laser microsurgery*. The Cochrane database of systematic reviews was also searched for relevant articles. Additional articles were identified by manually searching reference lists.

INTRODUCTION

Transoral laser microsurgery (TLM) is a minimally invasive surgical approach to functional organ preservation for cancer of the upper aerodigestive tract. It involves tumour resection using specialized endoscopic instruments, microscopes and lasers, with the wound bed often left to heal by secondary intention.[1] The term TLM was first coined by John Salassa of Mayo Clinic in the 1990s to distinguish this technique from the more generic endoscopic laser surgery by virtue of using an operating microscope to closely examine the host-disease interface following principles established by Wolfgang Steiner.[2] This affords the advantage of binocular vision and stereoscopic depth perception, combined with the superb optics of modern microscopes, making it truly a microsurgical technique. In contrast to non-surgical radiation and chemoradiation-based protocols, TLM places no limit on treatment options in the event of recurrent, persistent or second primary disease and avoids the long-term iatrogenic sequelae of definitive radiotherapy. TLM differs from traditional surgical oncology by departing from the classic Halstedian principle of *en bloc* resection. Instead, tumour is often divided with the laser and the tumour margin followed under the microscope, with frozen-section control, allowing piecemeal resection via the endoscope. The aim is to ensure a tumour-free margin in all dimensions with minimal excision of normal tissue. TLM also has a diagnostic element, as it precisely defines tumour extent at the time of surgery and provides maximal tissue for pathological assessment. Transoral minimally invasive techniques will likely become more widespread in the future as advances in technology continue to improve endoscopic access to the pharynx and larynx. This chapter describes the current state of surgical laser technology, its application to head and neck cancer, and provides a framework for the TLM approach to tumours at each major head and neck subsite.

LASERS

Production of laser light

An appreciation of the quantum physical basis of electromagnetic radiation is important for any surgeon wishing to understand the adjustable parameters of laser equipment. 'Laser' is an acronym for light amplification by stimulated emission of radiation. A laser consists of three key components: the lasing medium (e.g. carbon dioxide [CO_2]); an excitation source (e.g. alternating electrical current); and a resonant chamber with a mirror at either end to create positive optical feedback.

Laser energy is the result of electrons in the lasing medium transitioning from high to low energy states. Electrons are negatively charged subatomic particles that can be thought of as orbiting around a nucleus of protons and neutrons. Each orbit can be thought of as an 'energy level'. Electrons transition between discrete energy levels by either absorbing (low-to-high energy transition), or emitting (high-to-low energy transition) a packet of energy. Energy is emitted as a 'photon' of light, the wavelength of which may or may not be in the visible part of the spectrum. Electrons prefer to be in the lowest possible energy level, known as 'ground state'. The transition of an electron from a high energy level to ground state either occurs spontaneously or is stimulated by the collision of the atom with an incident photon. In the stimulated case, one photon collides with an atom and a second photon is emitted. The first photon is not absorbed and continues on its path. Therefore, the total number of photons is increased and the light is amplified.

The lasing medium is contained within the resonant chamber with a mirror at either end. The lasing medium is first excited ('pumped') with an input energy, usually an electrical current. This energy promotes electrons from their ground state to an excited state. Some electrons will then spontaneously fall back to ground state, emitting photons of light with a characteristic wavelength dependent on the lasing medium. These photons are reflected from the mirrors at the ends of the resonant chamber, back into the chamber. The photons will then collide with the lasing medium, producing stimulated electron transitions to ground state, and therefore stimulated photon emission. The stimulated emission has the same wavelength and travels in the same direction as the incident photon. For there to be net amplification of light, there needs to be more lasing medium molecules in the excited state than in the ground state at any one time. This state is known as 'population inversion' and is achieved by pumping with input energy. At one end of the resonant chamber the mirror is partially reflective and partially transmissive. Thus a portion of the light can escape the chamber as a 'laser beam'. The remaining light remains in the chamber, stimulating more photon emissions. The chamber rapidly reaches an equilibrium and the process continues as long as the excitation source maintains population inversion. The result is a beam of light that is monochromatic (of a single wavelength), collimated (travelling in one direction), and both temporally and spatially coherent (photons oscillate in phase, and are distributed equal and parallel across the wave front) (**Figure 22.1**).

Laser parameters

The adjustable parameters of surgical laser systems relate to the laser power, the size and shape of the focused beam (the 'spot'), the power output pattern (continuous wave (CW) or pulsed), and in some cases the equipment allows the user to specify a penetration depth. It is important to realize there is no single 'best' set of parameters: the most appropriate settings vary widely according to the clinical situation, the preferences of the individual surgeon, and between different laser delivery systems.

WAVELENGTH

The wavelength of laser light is dependent on the lasing medium. The CO_2 laser has been the workhorse of TLM since the inception of this approach to treating laryngeal carcinoma because of the excellent tissue cutting and coagulation properties.[2, 3] Other lasers such as Thulium-YAG and Holmium-YAG have been used for TLM and transoral robotic surgery.[4, 5] Each laser has a different wavelength and in turn different absorption characteristics in living tissues. The wavelength of the CO_2 laser is relatively long at 10.6 µm, placing it in the mid-infrared part of the electromagnetic spectrum. Therefore, CO_2 laser light is invisible. It is usually combined with a co-axial He-Ne red aiming beam. The CO_2 laser has a high coefficient of absorption by water, and its action is independent of

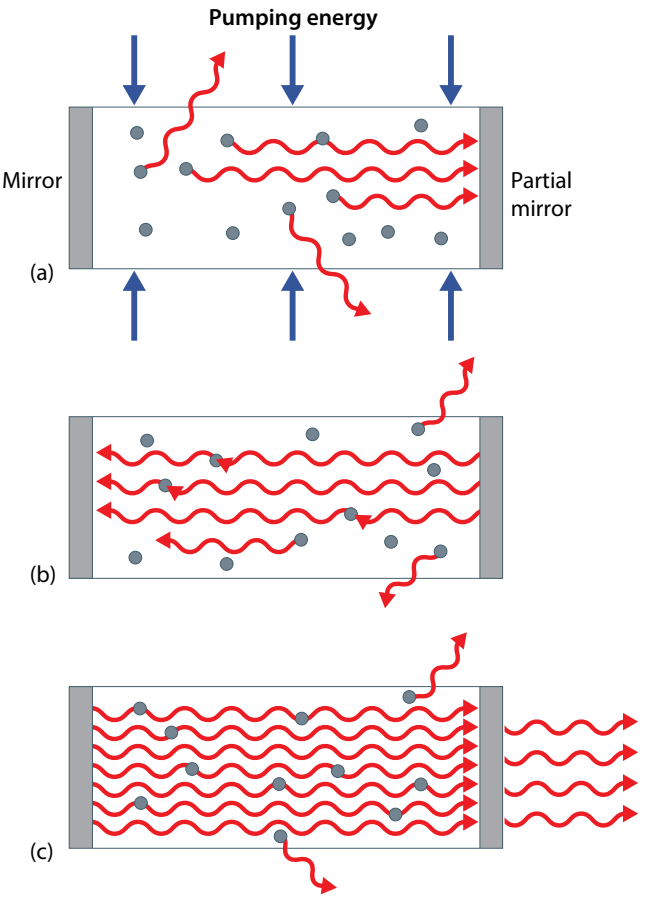

Figure 22.1 Laser physics. **(a)** Pumping of the CO_2 and start of the population inversion. **(b)** The reflected photons traverse the cavity and stimulate other CO_2 molecules to emit photons: the beam is amplified. **(c)** Almost the complete medium contributes to the stimulated emission. The laser beam is transmitted via the partially reflective mirror.

tissue colour. The energy of the CO_2 laser is therefore absorbed by all water-containing tissues.

POWER

Laser power (in watts) is a measure of energy (in joules) emitted per second. Increasing the power increases the amount of energy transferred to the target tissue per second. However, to predict the effect of a given power, the size of the focused beam and the pattern of power output must be known. That is because for a given power the effect on target tissues will be greater if the beam is focused onto a smaller spot (i.e. the energy is more concentrated in space). For this reason, it is sometimes useful to talk about 'power density' (in watts per cm^2) rather than power *per se* as means of comparing different laser set-ups. Similarly, for a given total amount of energy the effect is greater if it delivered over a shorter time period (i.e. the energy is more concentrated in time). Fluence (in joules per cm^2) is power density multiplied by the exposure time, and measures the *total* amount of energy delivered per unit area of exposed target tissue; the 'dose' of electromagnetic radiation. Some laser systems allow the user to specify a penetration depth. It is crucial to realize this is based on the *average* absorption of CO_2 laser light by living tissues. Based on this assumption of average energy absorption and knowing the size of the focused beam, the software calculates the power output required to make the selected incision depth. Therefore, by selecting an incision depth, the user is allowing the software to vary the laser power to produce a predicted surgical effect. The user should be aware that the system is by no means measuring the depth of the incision made, and the actual depth cut will depend on a variety of factors unique to each case.

FOCUSED BEAM 'SPOT' SIZE

The laser beam is passed through a lens to focus the energy on a spot which is typically 0.2–2.0 mm in diameter. The diameter of the focused beam exists over a range of distances around the focal length of the lens, the 'depth of focus'. By defocusing the beam the spot size at the target surface is increased and the laser energy is spread over a wider area. This effect can be exploited for haemostasis of small vessels up to 1 mm in diameter.[6] Larger vessels require careful identification and endoscopic clip application and/or cautery. As well as the manual microscope-mounted micromanipulator laser beam used in a standard 'dot-to-dot' approach, some surgeons use the AcuBlade™ system (Lumenis Inc., Santa Clara, CA., USA). This automatic scanning micromanipulator system produces either linear or curvilinear incisions or circular areas of tissue ablation by rapidly scanning the laser beam back and forth along a pre-determined path.[7]

POWER OUTPUT PATTERN

Lasers energy can be delivered through intermittent pulses, repeated pulses, as a continuous wave (CW) or as very rapid (< 1 ms) pulses in the form of UltraPulse of SuperPulse mode. CW mode produces surrounding tissue damage from thermal spread of laser energy. To produce the desired effects of cutting and coagulation with adequate haemostasis of small vessels and limited char formation, specialized CO_2 laser pulsed modes have been developed: SuperPulse and UltraPulse. These are used with the laser in CW mode, with the energy output pattern modulated into a SuperPulse or UltraPulse pattern. Pulsed modes deliver high peak power density in repeated short duration (< 1 ms) pulses. The difference between SuperPulse and UltraPulse is subtle and clinical outcomes are largely equivalent, although incisions are marginally finer with UltraPulse mode.[7] Superpulse has higher peak energy, less total energy per pulse and more rapid pulse repetition compared to UltraPulse.[6]

Delivery systems

Until relatively recently the CO_2 laser was limited to line-of-sight delivery via a reflecting mirror driven by a micromanipulator mounted on an operating microscope in the manner first used by Strong and Jako in 1971.[3] Restrictions in the physical workspace available via the transoral route, and/or in laryngeal exposure limited the circumstances in which the CO_2 laser could be used. Hollow waveguide systems have been developed to allow the CO_2 laser to be delivered via flexible guides to an increased range of upper aerodigestive tract subsites. These flexible waveguides can be used freehand using a variety of hand pieces, linked to a transoral robotic system, or used via flexible endoscopes in an outpatient setting.[8–15] The first hollow core flexible waveguide system was developed by OmniGuide (Boston, MA., USA) using a photonic band-gap fibre assembly, and is now marketed as BeamPath™. Subsequently, Lumenis (Santa Clara, CA., USA) have developed the FiberLase™ system.

Laser interaction with tissues

When laser light hits tissues, a proportion of the energy is reflected from the surface, a proportion is scattered, a variable amount is absorbed, and the remainder is transmitted. Reflected energy is effectively lost for the surgical purpose of cutting and coagulation and can cause unwanted thermal injury to adjacent tissue. Scattering is dependent on the optical properties of the tissue and the wavelength of light. Shorter wavelengths are scattered more than long wavelengths; hence the commonly used CO_2 laser in TLM is only minimally scattered. Absorption requires a chromophore (a molecule to absorb energy at a particular wavelength). In the case of the CO_2 laser the chromophore is water. The intensity of laser energy decreases exponentially from the tissue surface, hence the absorption (and therefore the heat generated) is maximal at the tissue surface. The thermal penetration of the CO_2 laser is much shorter than other lasers; several micrometres compared to several millimetres for Nd-YAG, Argon, or KTP-YAG lasers.[16, 17] Laser energy is rapidly converted

to heat, resulting in tissue vaporization and precise cutting. Compared to other lasers, the CO_2 laser causes much less thermal spread to adjacent tissues.[18] It is important to maintain appropriate tissue traction and counter-traction when working with the CO_2 laser, to allow visualization of the cut tissue surface and to avoid excessive char formation. In contrast to tumour excision by cutting with a CO_2 laser, there has been some early success with photoangiolytic therapy for early glottic carcinoma.[19–22] In this technique, a KTP laser or other angiolytic lasers that use haemoglobin as a chromophore are exploited to selectively destroy the microvasculature of early glottic cancers.

OPERATING ROOM SET-UP

Trans-oral techniques require a number of highly specialist pieces of equipment including the operating microscope, endoscopes, lasers and endoscopic graspers, diathermy probes and clip applicators. The arrangement of the room is an important consideration since the microscope and laser are bulky and there are specific safety concerns regarding the laser and operating room personnel. **Figure 22.2** is a schematic representation of the typical operating room set-up. It is important to have a selection of endoscopes available (**Figure 22.3**). A good endoscope has a wide proximal aperture to allow instruments to be introduced and manipulated to achieve optimal tumour exposure and tissue retraction. Some endoscopes have inbuilt smoke extraction ports whilst others require an additional smoke extraction unit to be mounted. For oropharyngeal and some hypopharyngeal tumours, the Feyh-Kastenbauer retractor (Invotec) may be used (**Figure 22.4**). This is a highly versatile system, and provides excellent exposure in the majority of cases. Several laser delivery systems are available, each with their own specific advantages and disadvantages over others. The most commonly used systems include the microscope-mounted micromanipulator and more recently flexible hollow core delivery systems (**Figure 22.5**). In all cases, the back table is set up with a selection of endoscopic graspers and diathermy probes (**Figure 22.6**). For dental protection, we prefer to use customized guards for each patient, made from thermoplastic (**Figure 22.7**).[23]

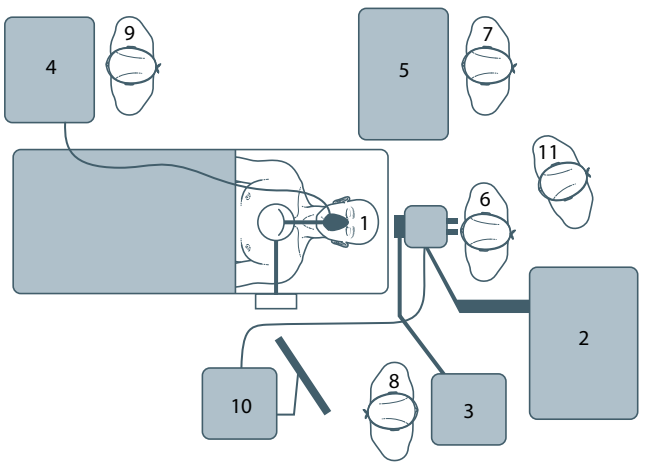

Figure 22.2 Operating room layout. 1, Patient positioned on operating table, with laryngoscopy suspension in place. 2, Operating microscope. 3, Laser coupled to the microscope-mounted micromanipulator. 4, Anaesthetic machine. 5, Back table. 6, Operating surgeon. 7, Operating room nurse at the back table. 8, Operating room nurse controlling the laser. 9, Anaesthetist. 10, Endoscopy 'stack' with camera coupled to the microscope. 11, Trainee surgeon.

HANDLING THE PATHOLOGIC SPECIMEN

A fundamental concept in TLM that distinguishes it from traditional surgical oncology is resection by tumour division. There is now extensive clinical and experimental evidence showing no compromise of local oncologic control with a systematic TLM piecemeal resection compared to the traditional *en bloc* approach.[2, 24–26] The host–disease interface is carefully examined under the operating microscope and the tumour removed piecemeal through the endoscope. For early glottic carcinoma, UK TLM surgeon consensus agreement is for circumferential or *en bloc* resection where feasible with the philosophy of a second-look surgery in the event of uncertain or positive margins.[27] As the indication for TLM evolves to include larger tumours in more inaccessible subsites the paradigm for dealing with resection margins is also changing. The complete excision of tumour to negative histopathological margins at the primary site is key to local disease control.[28, 29] Positive margins on permanent section at the end of TLM are associated with significantly increased rates of local recurrence, distant metastasis, and necessity for salvage surgery, as well as lower overall survival rates.[26, 30] However, an advantage of TLM is that there is usually no need to reconstruct the surgical defect, so the tumour bed is left exposed and readily accessible for second or even third resections to achieve negative margins. There is no negative effect on local recurrence or survival if the negative margin requires two or more attempts.[28, 29]

Hinni et al. recently coined the term 'margin mapping' to describe their approach to the pathological specimen in a series of 128 TLM oropharyngeal cancer resections.[31] This technique involves the surgeon inking the margins of each section of the tumour removed in the operating theatre followed by careful pathological assessment of the margin by intra-operative frozen section. Overall, the positive deep margin rate in the permanent section was 1% for previously untreated palatine tonsil squamous cell carcinoma. There were no local recurrences in the previously untreated group. The piecemeal removal of tumour in the lateral oropharynx is therefore oncologically sound. This is despite what some would term 'close' margins, with the mean smallest margin of 1.98 mm. Hinni et al. relate the size of the deep margin to the width of the lateral oropharyngeal wall musculature in healthy volunteers as assessed by magnetic resonance imaging and conclude

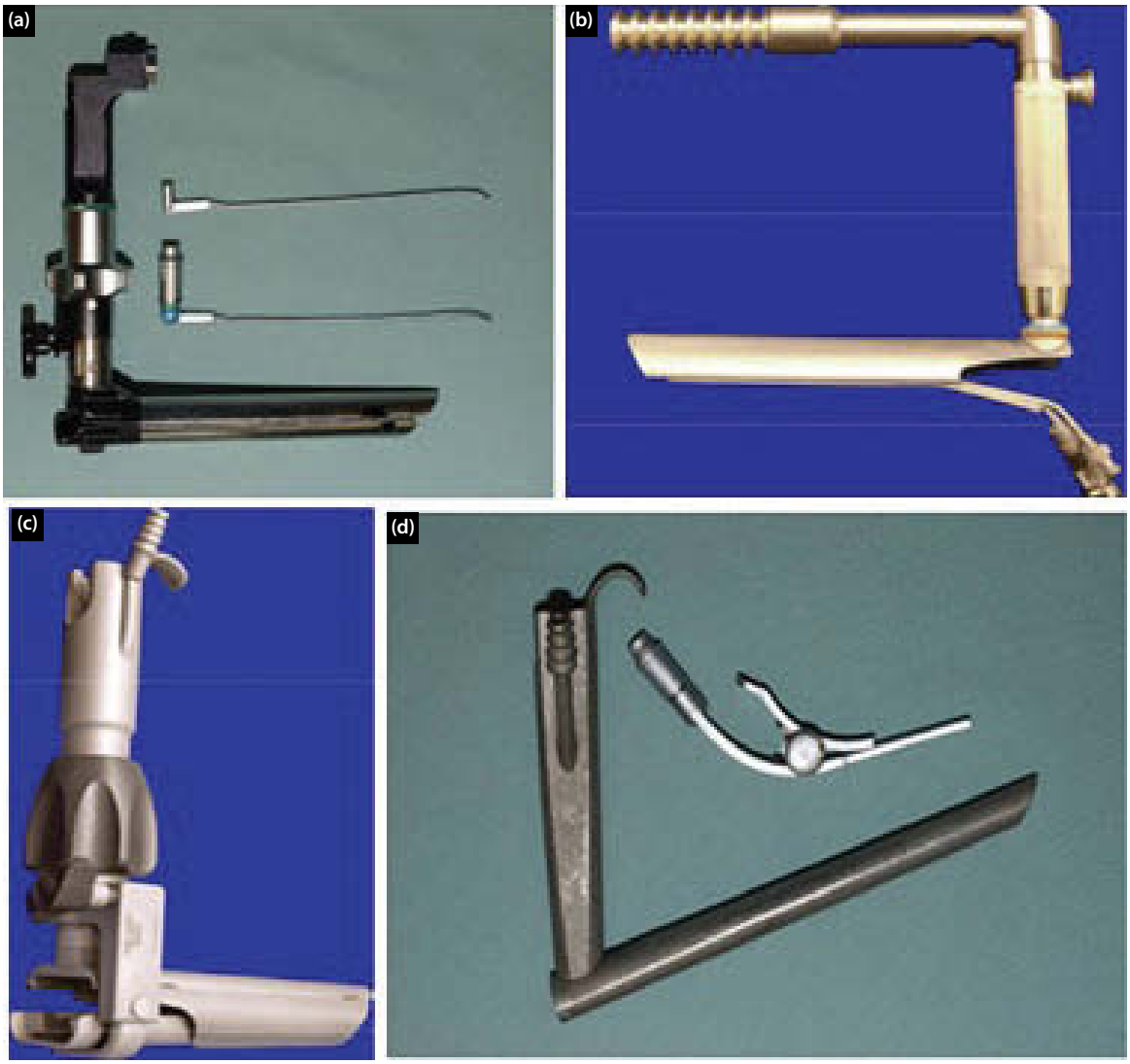

Figure 22.3 Endoscopes used in TLM. **(a)** Steiner distending laryngoscope. **(b)** Zeitels universal modular laryngoscope. **(c)** Steiner distending oropharyngoscope (supraglottiscope). **(d)** Steiner laryngoscope.

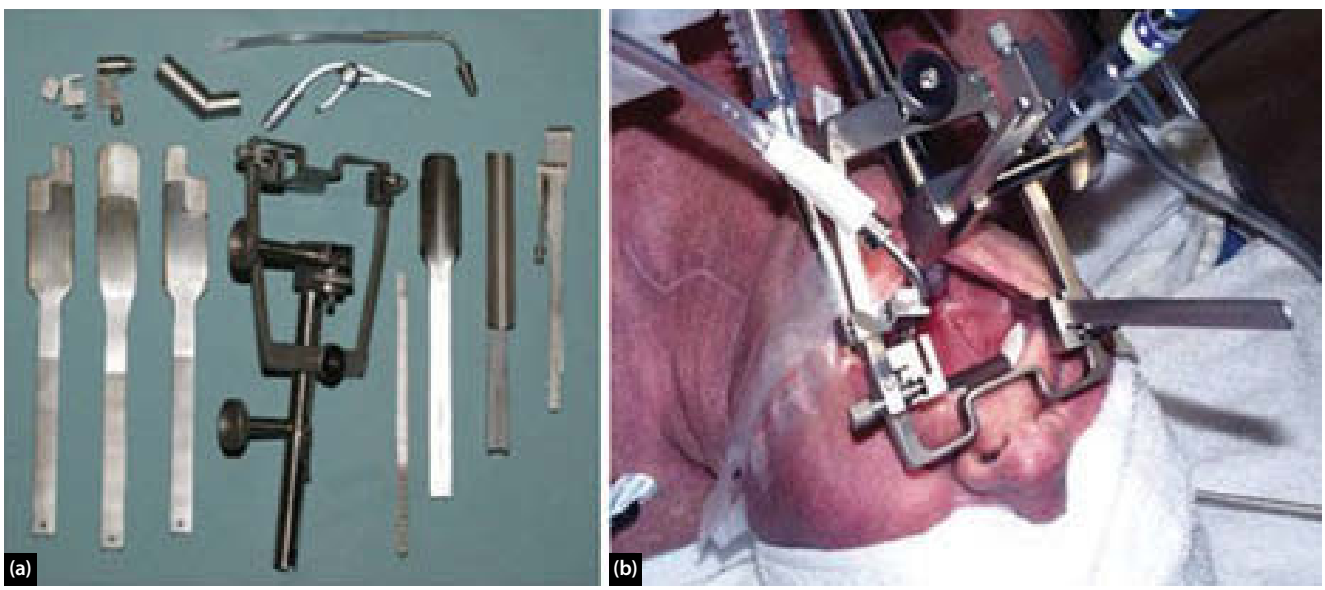

Figure 22.4 Feyh-Kastenbauer retractor set. **(a)** Retractor set **(b)** Retractor placed in the mouth prior to a transoral resection. Assembled *in situ*.

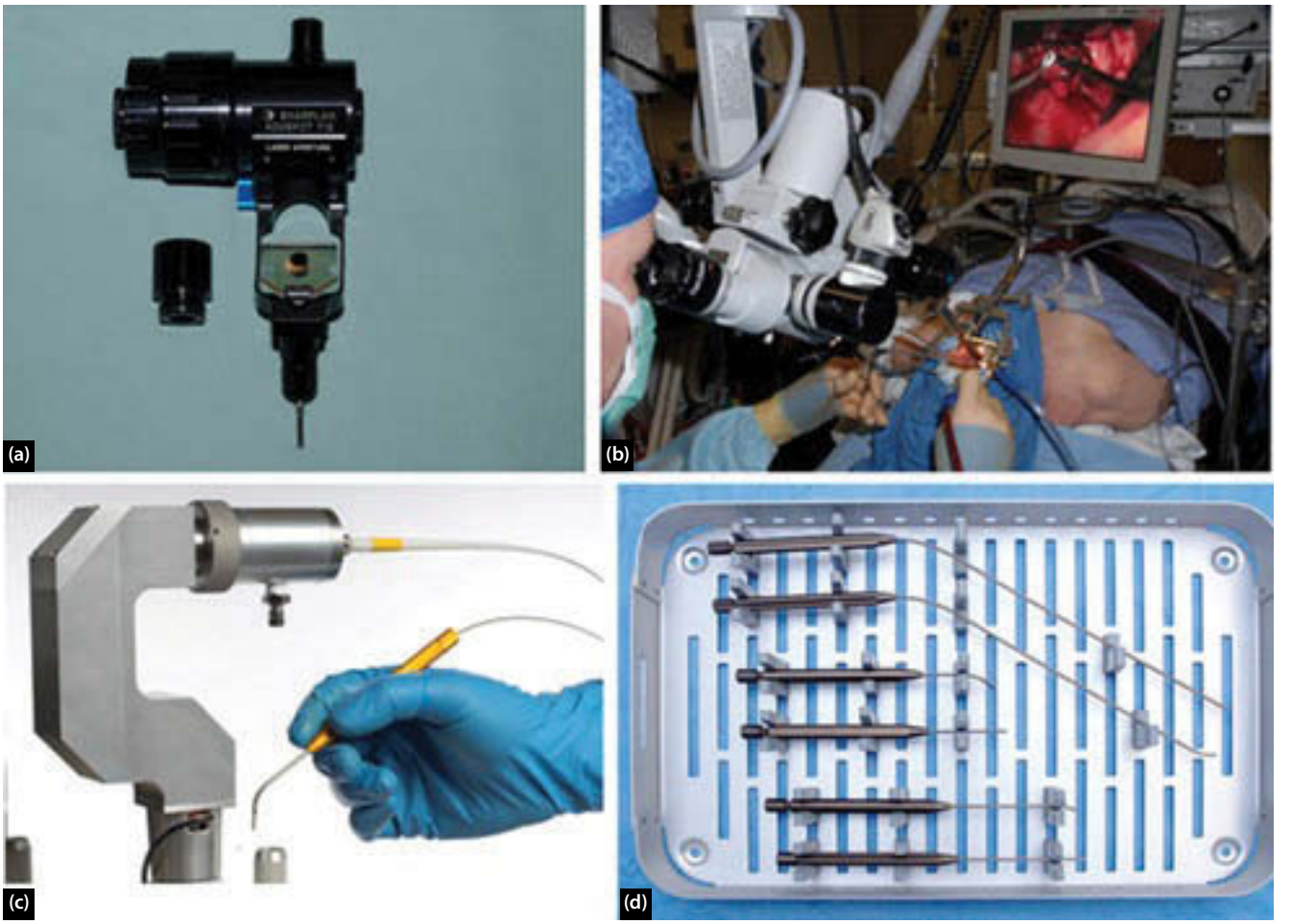

Figure 22.5 Laser equipment. **(a)** Microscope mounted micromanipulator. **(b)** The micromanipulator in use. **(c)** Hollow core flexible waveguide (Omniguide Inc.). **(d)** A selection of handpieces for the flexible laser delivery system.

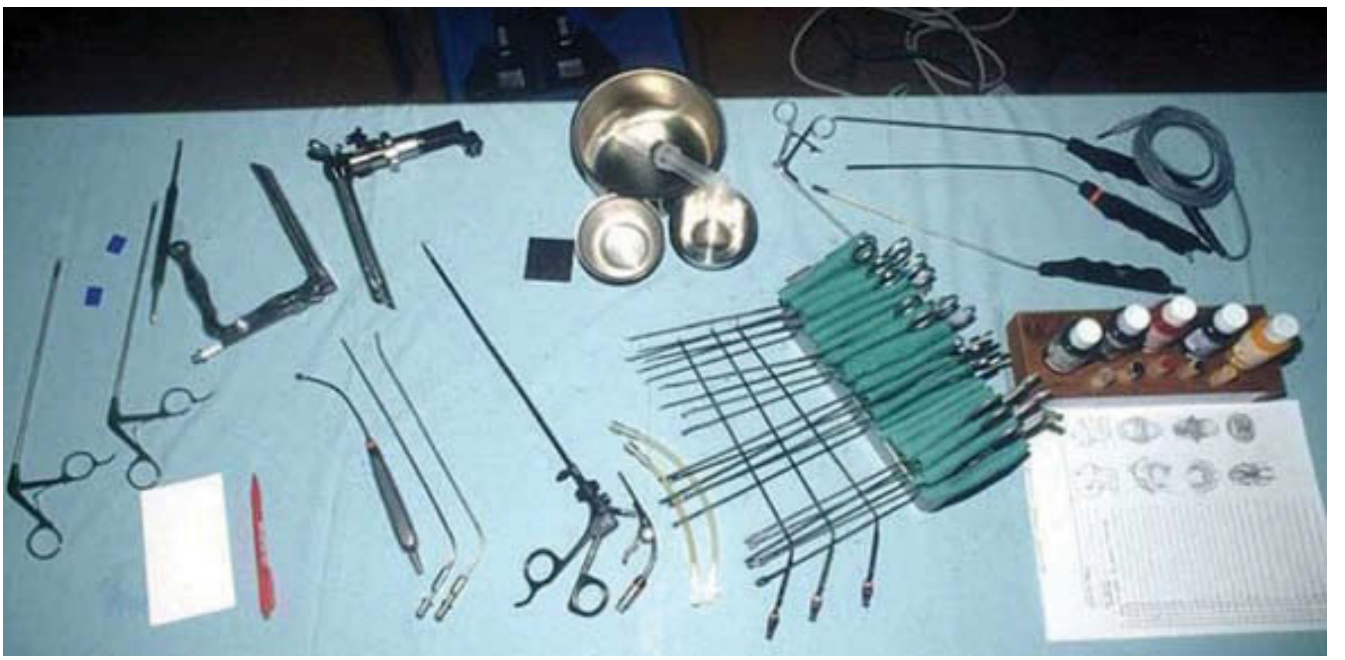

Figure 22.6 The back table. The set-up includes a variety of graspers, diathermy probes and an inking set for intra-operative margin marking.

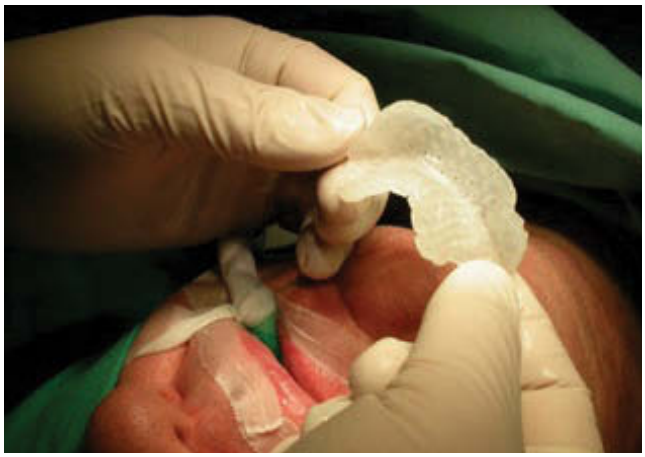

Figure 22.7 Custom dental protection. We favour the use of custom-made mouth guards in thermoplastic.

Figure 22.8 The tongue is non-compressible. Illustration of the difficulty of endoscopic exposure imposed by a large tongue, here using a tennis ball as the 'tongue'.

that since the superior constrictor width is 2.4 mm, it is unlikely that larger margins would be obtainable. They point out that inferiorly in the tonsillar fossa, deep to the superior constrictor muscle, is a space between styloglossus and stylopharyngeus muscles filled with parapharyngeal fat. This fat is unlikely to represent a barrier to tumour spread and is of no use as a frozen section margin. It should be emphasized that this detailed microscopic 'margin mapping' approach requires close collaboration between the surgeon and pathologist for intra-operative frozen section analysis and reporting. In some institutions limited resources mean this is simply not practicable.[32] It is also important to remember that frozen sections do not always correlate with permanent pathology.[33]

OPERATIVE TECHNIQUE

General considerations

The optimal patient for TLM is edentulous, with a wide mandible and no limitation of neck extension. Patient selection is key to the success of the technique, as inadequate endoscopic access to facilitate satisfactory oncologic resection is the main contraindication to TLM. It is important to realize that it is often necessary to adjust the set-up at least once during the procedure. Be prepared to change the endoscope and to move position to facilitate tumour exposure and extirpation. The tongue can be a source of significant difficulty in achieving the optimal exposure, as it is non-compressible (**Figure 22.8**). In addition, prolonged retraction and compression of the tongue can result in post-operative complications such as lingual and hypoglossal nerve palsies, and tongue oedema necessitating tracheostomy. In short, the usual caveats of endoscopic exposure apply to the TLM technique: think of the five Ts, Tongue, Trismus, Teeth, Tumour and Tilt (neck extension). To some extent, the development of flexible hollow-core waveguide systems for CO_2 laser delivery has allowed the endoscopic surgeon to work around corners; however, the microscope-mounted laser is limited to line-of-sight view. Therefore, appropriate tissue retraction and positioning of endoscope blades is essential for efficient and effective surgery. The optimal technique involves retracting the tumour into the field of view, applying tension to the specimen and cutting with the laser along the host–disease interface. The use of robotic techniques partially obviates this limitation, but sacrifices the magnification benefits of the TLM procedure.

As with any technique, experience is an important factor in the outcome. In particular, the ability to operate on larger tumours with the TLM approach is experience-dependent. There is a significant learning curve that affects both oncologic outcome and the incidence of operative complications.[34, 35] The authors recommend gaining experience on small tumours before attempting more complex resections using TLM. Locally-advanced hypopharyngeal tumours are often beyond the surgical expertise of even the most experienced TLM surgeons.

Laryngeal carcinoma

The aim of TLM is to preserve as much normal tissue as possible, thereby maximizing the potential for functional recovery. Small superficial T1a glottic tumours may be excised *en bloc* with the CO_2 laser.[27] More complex glottic and supraglottic tumours (T1b, T2-T3) benefit from an initial cut through tumour to assess depth of invasion (**Figure 22.9, Figure 22.10,**). The way in which the laser cuts through normal tissue and tumour is very different and can be appreciated under the operating microscope Normal tissues under tension will spring apart with a 'clean' appearance. Tumour tends to be firmer, less elastic and chars more when cut with the laser. Once the deep margin of the tumour is identified, the host–disease interface is followed with the laser and the tumour removed piecemeal. For large exophytic tumours, the authors recommend initially debulking the tumour to allow accurate assessment of the tumour footprint and its interaction with the host tissues. Assessment of the tumour should take into account the functional consequences of resection.

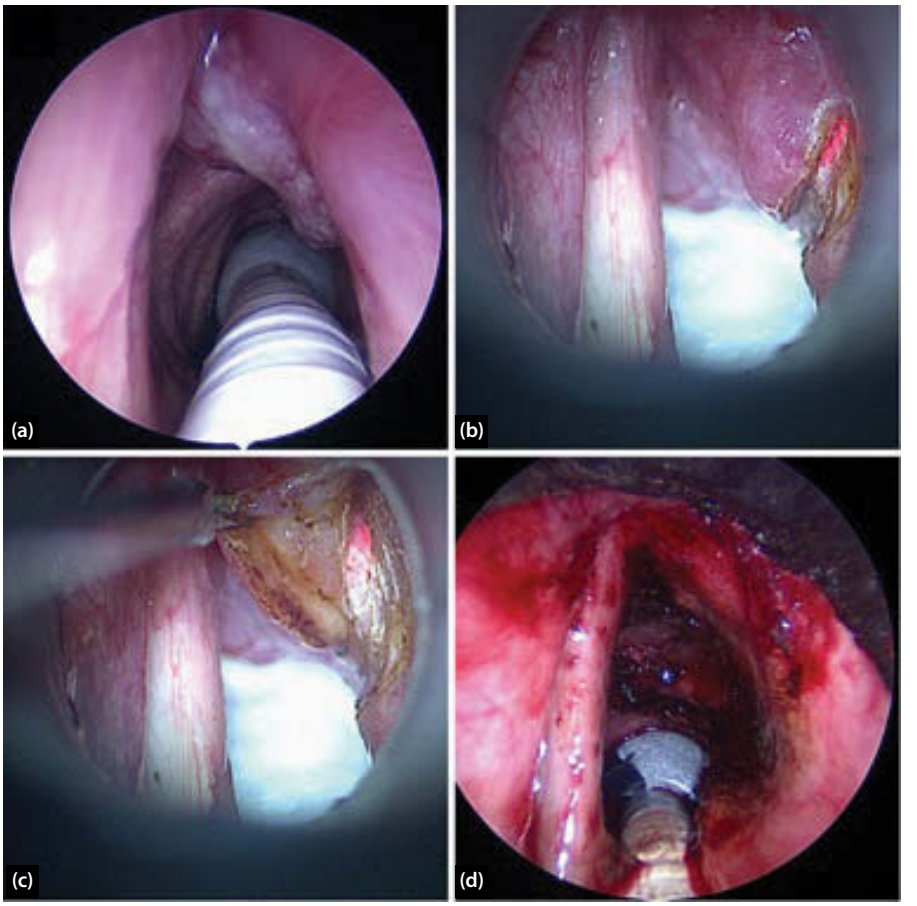

Figure 22.9 TLM for T1a N0 glottic carcinoma. **(a)** Tumour is confined to the right vocal cord. **(b)** The tumour is first divided with the laser to assess the depth of invasion. **(c)** The deep margin of the tumour is followed with the laser, applying tension to the specimen. **(d)** Appearance at completion of resection.

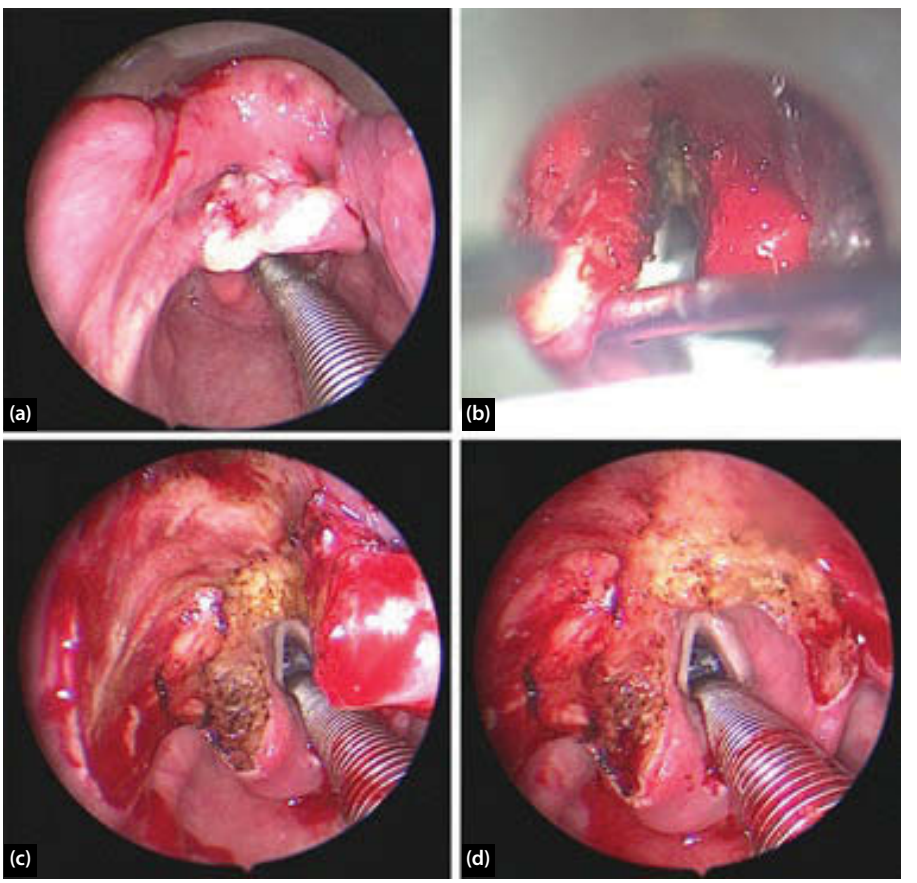

Figure 22.10 TLM for T2 N0 supraglottic carcinoma. **(a)** T2 tumour involving the epiglottis. Both arytenoids are free of tumour. **(b)** The epiglottis is first divided vertically to split the tumour in two to assess depth of invasion. **(c)** The left supraglottis is removed first. The arytenoid is spared. **(d)** Appearance at completion of resection.

To prevent significant functional impairment at least one competent arytenoid complex should be preserved.

The major limiting factor in TLM is surgical access. It has been the experience of the authors that laser excision of the false cord is useful for endoscopic access to the underlying glottis in some cases. Almost any laryngoscope can be used, and several different scopes may be needed during one resection. Very small diameter scopes such as the Hollinger laryngoscope may afford only a monocular view. Deployment of the laser in this situation is difficult. Laryngoscopes with matt finishes are preferable, as this limits reflections from the microscope. For glottic and supraglottic laryngeal carcinoma TLM, the authors prefer the use of suspension with the Göttingen table (Karl Storz). This modular system allows great flexibility and is ideal for laser laryngeal surgery (**Figure 22.11**).

Oropharyngeal carcinoma (OPC)

The use of TLM as a treatment for OPC was first reported by Steiner et al;[36] however, its use was been widely adopted until recently when evidence emerged of its potential benefits in treating OPC with the aim of achieving improved post-treatment swallowing function.[37–39] This is particularly pertinent in this era of HPV16 + OPC as TLM has the potential to contribute favourably to treatment de-intensification strategies. (See Chapter 13, Oropharyngeal tumours)

Transoral access to the lateral oropharynx and the soft palate is relatively straightforward using either a standard Boyle Davis tonsillectomy gag or, more usually, a Feyh-Kastenbauer retractor (**Figure 22.4**) or equivalent. In contrast, access to the tongue base is challenging. Access, if secured at all, is usually achieved using a bivalved distending oropharyngoscope (**Figure 22.3a**). Even then, due to the line-of-sight constraints, complete exposure of the tumour is not the norm and tumour resection has to proceed in a superficial to deep direction, appreciating the 3D orientation of the base of tongue and vallecula. In addition, it may be difficult, even for experienced surgeons, to distinguish tumour from normal base of tongue lymphoid tissue. In such cases, frozen section assessment may be helpful.

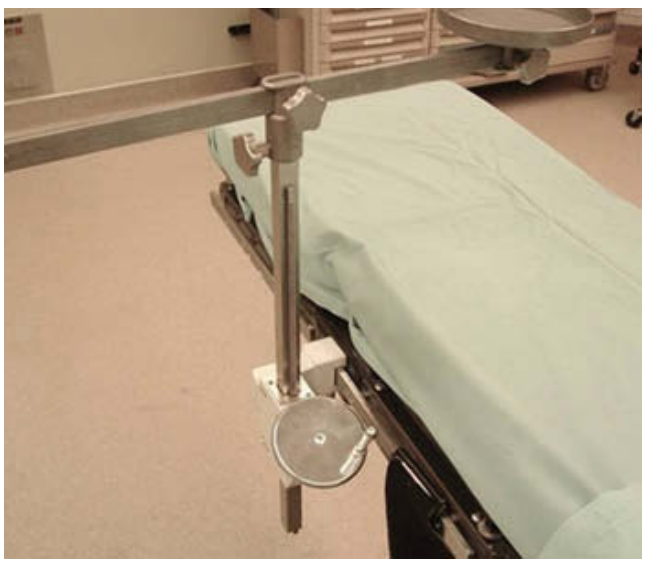

Figure 22.11 Göttingen suspension table. Adjustable laryngoscopy suspension table used for TLM resections. This offers maximal flexibility.

When resecting a tonsil carcinoma, following adequate exposure, it is usual to start by transecting the tumour in the axial plane at the mid-point, immediately separating the tumour into a superior and inferior portion.

Each portion is then resected completely, paying particular attention to the mucosal and deep margins whilst considering the trade-off between normal tissue resection and complete tumour removal.

It is important to appreciate, as highlighted above, that there is an anatomical limitation to the extent of deep resection margin that can be achieved in many cases.

Following resection of the main tumour specimen – which is typically orientated and pinned to a cork-board – and in the absence of frozen section availability, representative marginal biopsies are taken from the mucosal edges and deep tissues of the tumour bed. These marginal biopsies are separately assessed for the presence of residual tumour. There should be a zero tolerance for positive marginal biopsies and further resection should be mandated for the infrequent cases where one or more marginal biopsies are positive for tumour.

Similar resection margins are taken following the resection of tongue base tumours although the position from which the marginal biopsies are taken is less proscriptive and is tailored to the position and extent of the primary tumour resection. Despite this, the same zero tolerance for positive marginal biopsies should be maintained.

Hypopharyngeal carcinoma

The same principles of TLM apply when using it to treat cancers of the hypopharynx. As highlighted above, the management of large hypopharyngeal tumours using TLM is contraindicated in all but the most experienced hands. However, TLM removal of smaller tumours (T1/2) is often surprisingly straightforward and results in highly favourable swallowing function outcomes. Assuming there are no anatomical limiting factors relating to the jaw and dentition, access to tumours in the hypopharynx, using a distending oropharyngoscope, is often more straightforward than accessing the more constricted and anteriorly placed larynx – particularly if the tumour is anteriorly placed within the larynx.

An absolute contraindication to TLM in the hypopharynx includes tumour invading through thyroid cartilage into the tissue of the neck and relative contraindications include large tumours, the resection of which will also include the hemilarynx.

COMPLICATIONS

As the indications for TLM to treat laryngeal and pharyngeal malignancies have increased, so too has the number

of complications.[35] Although there are many advantages of TLM over traditional open surgical approaches, such as a decreased need for tracheostomy and gastrostomy with improved post-operative speech and swallowing function, it is not without risk of significant intra-operative and post-operative complications. Routine laser safety precautions are observed to reduce the risk of inadvertent burns to the patient and operating theatre staff. The patient's eyes and face must be covered with wet towels soaked in saline and all operating theatre personnel (with exception of the operating surgeon) must wear protective eye-glasses. It is common practice to display notices outside the operating theatre to warn staff the laser is being used.[40] The major procedure-associated risks are intra-operative airway fire, post-operative haemorrhage and aspiration pneumonia.

Upon contact with living tissue the energy in the CO_2 laser is immediately converted to heat, reaching temperatures up to 450 °C. The incidence of airway fire in large series is 0.4–1.5%.[41] The time to ignition of fat when lasing in oxygen concentrations of > 50% and with a power greater than 5 W is less than 5 seconds.[41] TLM is typically performed with FiO_2 < 30%, especially if an open ventilation system such as high-frequency jet ventilation is used, to avoid significant risk of airway fire.[6, 41, 42] It is routine practice to use laser-compatible endotracheal and jet ventilation tubes, and to cover the cuff of the endotracheal tube with saline-soaked patties to reduce the chance of tube damage and airway fire.[43] Smoke exhaustion should always be used, as the combustible particles in smoke significantly increase the chance of ignition at the site of lasing.[41] In the event of an airway fire the endotracheal tube is removed, the airway re-secured, bronchoscopy is performed and the procedure is terminated.

The most worrisome post-operative complication following TLM is catastrophic haemorrhage in the presence of impaired swallowing and airway protection. In this scenario patients are at risk of death from both torrential aspiration and exsanguination.[35, 44, 45] Rates of post-operative bleeding in large series are 1.4–10%.[1, 44, 46] The majority of bleeds occur within 7 days of surgery, but late secondary haemorrhage occurring up to 17 days post-operatively has been reported.[44] Bleeding is more likely in lateral pharyngeal wall and supraglottic resections compared to resections limited to the endolarynx or oral cavity.[44] Post-operative haemorrhage after TLM highlights the need for modern head and neck surgeons to be familiar with neck vascular anatomy from an inside-out perspective, in contrast to the traditional outside-in view (**Figure 22.12**). Larger vessels should be carefully identified, and clipped and cauterized before division. Vessels identified as the source of major post-operative secondary haemorrhage include the superior laryngeal artery, lingual artery and anterior facial artery.

It is preferable for the TLM surgeon to manage any post-operative haemorrhage. The principles are those of securing and preserving the airway and controlling the source of bleeding. If a surgeon other than the TLM surgeon is managing the emergency situation it may be safer to tie off the external carotid system in such cases, or consider endovascular embolization. Small bleeds should be considered sentinel bleeds. A careful and thorough endoscopic examination under anaesthesia in theatre by the TLM surgeon with equipment available to deal with a major haemorrhage (large clip applicators, large-bore suction, and monopolar and bipolar diathermy) may be required.

ADDITIONAL CONSIDERATIONS

Compared to traditional open surgery, TLM greatly reduces the need for tracheostomy and tube feeding.[47, 48] Temporary tracheostomy may occasionally be necessary for some patients undergoing extensive resections in whom significant aspiration is expected in the immediate post-operative period and who have marginal pulmonary function. Other indications for tracheostomy in TLM cases include patients with high risk of post-operative haemorrhage, and those who have received prior radiotherapy and undergo concurrent neck dissection at the time of TLM resection. Tracheostomy may also be necessary on occasion to improve endoscopic access to the tumour by obviating the oro-tracheal tube. It must be borne in mind, though, that tracheostomy impairs swallowing function in the immediate post-operative period. In the setting of post-operative complications necessitating a return to the operating room, it may be preferable to perform a tracheostomy, to avoid trauma to the healing surfaces by intubation and subsequent extubation by an oro-tracheal route.

Feeding tubes are generally not required in TLM resections. In some extensive oropharyngeal and supraglottic resections it may be necessary to place a nasogastric tube temporarily. This is best done by the operating surgeon under direct vision at the time of TLM resection. In the presence of large open wounds with multiple vascular clips the patient should remain nil by mouth for a period after surgery to reduce the risk of post-operative haemorrhage. In patients requiring post-operative radiation therapy and predicted to require a feeding tube for a prolonged period, the naso-gastric tube should be converted to a percutaneous gastrostomy tube if possible. Early involvement of a specialist speech and language therapist is of benefit for patients with swallowing impairment.

Other considerations include elective intensive care unit admission and the use of antibiotic prophylaxis during healing. Generally, ICU admission should be considered in patients at high risk of post-operative haemorrhage and those requiring tracheostomy. Some TLM surgeons favour the use of post-operative antibiotics in selected cases. It is our routine practice to avoid the use of antibiotics in the majority of patients.

CONCLUSIONS

The continued development of endoscopic and laser equipment has enabled significant advances in minimally invasive surgical approaches for head and neck cancer. TLM offers an alternative to traditional open surgical approaches, with minimal reconstruction (and the associated morbidity)

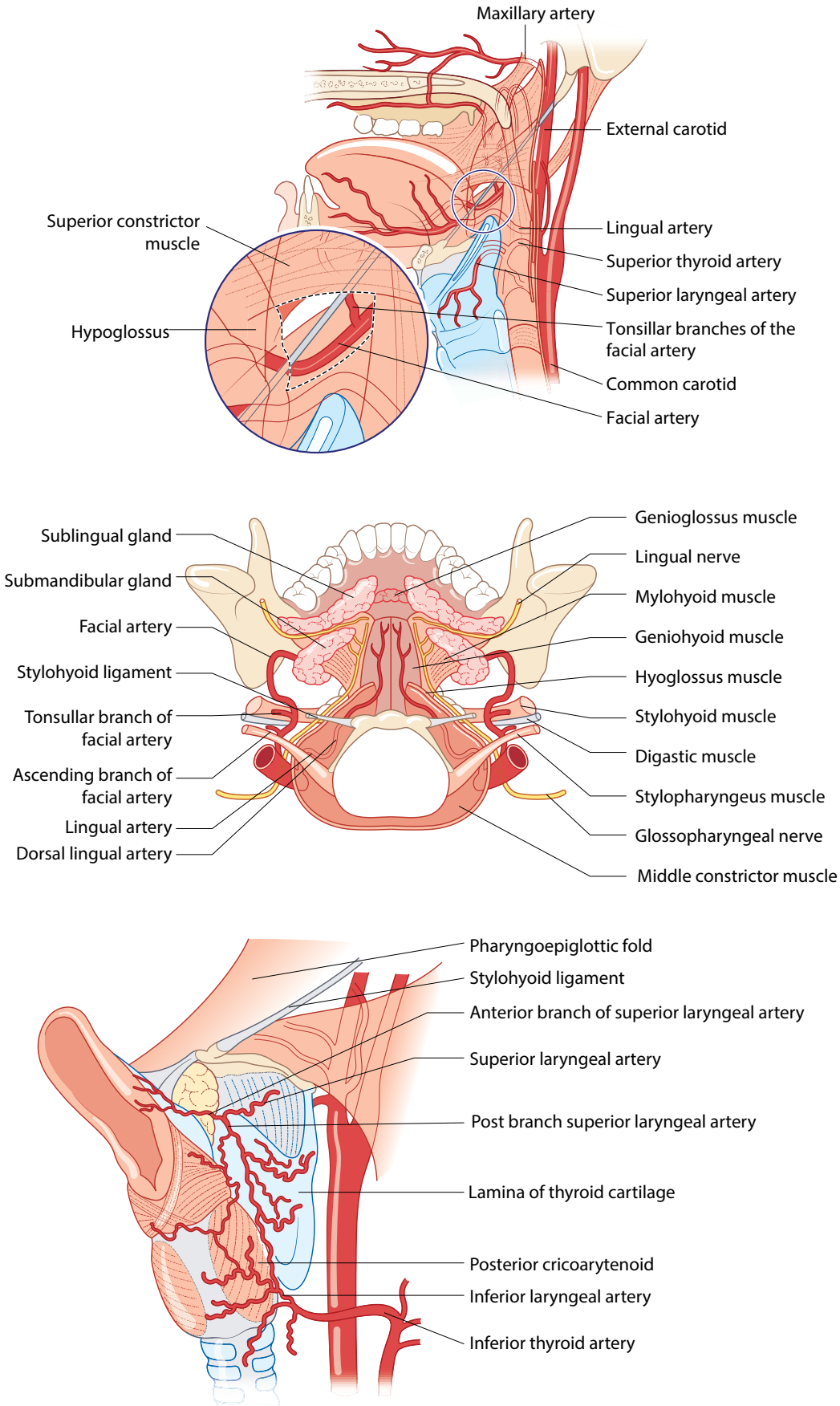

Figure 22.12 Vascular anatomy for TLM.

required in the majority of cases. Since its introduction in the 1980s the use of TLM has expanded to include all head and neck subsites. This is the result of technological advances in both endoscopic access and methods of delivering laser energy to the tumour site, combined with a developing surgical experience and expertise throughout Europe and North America. An understanding of the equipment required to achieve optimal surgical access and the pertinent factors influencing patient selection are key for the practice of TLM. Surgeons of the future need to familiarize themselves with the operating room set-up and operative technique of TLM throughout their training to offer this approach as part of a modern and integrated multidisciplinary head and neck cancer service.

KEY POINTS

- Transoral laser microsurgery is a proven technique in the management of the primary site for a variety of cancer subsites in the upper aerodigestive tract.
- This technique offers significantly less morbidity compared to open approaches.
- The technique requires surgeons to have an excellent appreciation of the anatomy from inside out.
- Significant research is ongoing on transoral surgical techniques with improvements in instrumentation and increased experience.

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CHAPTER 23

ANATOMY AS APPLIED TO TRANSORAL SURGERY

Mark Puvanendran and Andrew Harris

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SEARCH STRATEGY

The data in this chapter is supported by a Medline search using the keywords: transoral surgery, tongue, pharynx, and larynx.

INTRODUCTION

Anatomy is traditionally taught through an outside-to-inside approach. Transoral laser microsurgery (TLM) and transoral robotic surgery (TORS) challenge this classical view, necessitating a 3-dimensional appreciation of the relevant anatomy from a counter-intuitive, inside-out approach. This is particularly important as tumour and/or surgical instrumentation such as retractors or endoscopes distort the normal anatomy. While other chapters within this reference text offer the conventional anatomic approach, the aim of this chapter is to focus on head and neck anatomy relevant for TLM and TORS, with special relevance to the vascular anatomy as seen from a transoral perspective.

TONGUE BASE

The tongue base refers to the posterior portion of the tongue (oropharynx), separated from the anterior, oral cavity segment by the terminal sulcus. This area is derived from the second, third and fourth branchial aches. The tongue base contains the lingual tonsils and the pharyngoepiglottic and glossoepiglottic folds (**Figure 23.1**).

Muscles

The tongue is composed of intrinsic and extrinsic muscles, the muscles on each side are separated by a dense fibrous midline band. The intrinsic muscles from superficial to deep are: superior longitudinal, inferior longitudinal, transverse and vertical. These muscles generally serve to alter the shape of the tongue, the intrinsic muscles are all innervated by the hypoglossal nerve.

The intrinsic and extrinsic muscles of the tongue and their relationship with the oral cavity can be appreciated in **Figure 23.2**.

There are four extrinsic tongue muscles, originating from outside the tongue and inserting within the substance of the tongue. They are styloglossus, hyoglossus, genioglossus and palatoglossus. These are paired muscles which move the main body of the tongue. A detailed breakdown of the actions of the muscles is in the **Table 23.1** below.

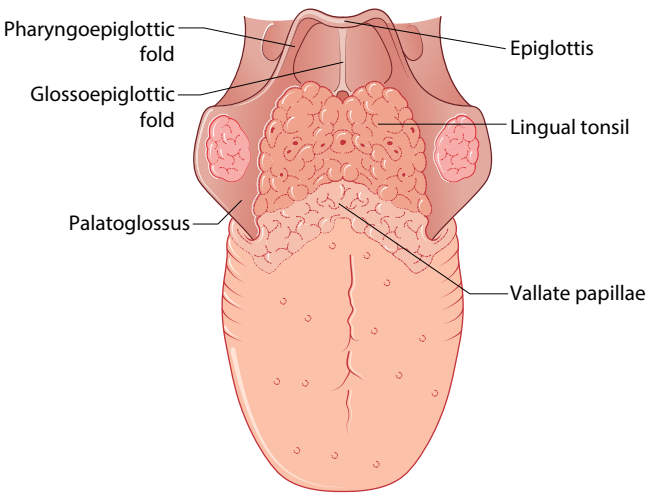

Figure 23.1 Tongue surface anatomy.

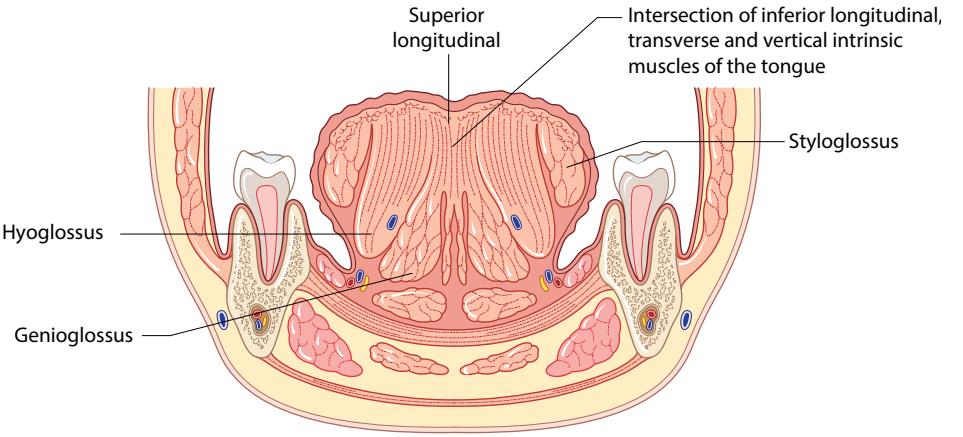

Figure 23.2 Cross-sectional anatomy of the tongue highlighting the muscles of the tongue.

TABLE 23.1 Anatomy, innervation and action of tongue muscles

Muscle	Type	Origin	Insertion	Action
Superior Longitudinal	Intrinsic	Lingual septum and submucous fibrous layer	Margins of tongue	Elevates tip and sides of tongue; shortens tongue
Inferior longitudinal	Intrinsic	Body of hyoid and base of tongue	Apex of tongue	Curls tip inferiorly; shortens tongue
Transverse	Intrinsic	Lingual septum	Submucous fibrous layer	Narrows and lengthens tongue
Vertical	Intrinsic	Superior surface of the tongue	Inferior surface of tongue	Flattens and broadens tongue
Genioglossus	Extrinsic	Mental spine of mandible	Lateral and inferior tongue	Depresses and protrudes tongue
Hyoglossus	Extrinsic	Body and greater horn of hyoid	Lateral and inferior tongue	Depresses and retracts tongue
Styloglossus	Extrinsic	Styloid and stylohyoid ligament	Lateral and inferior tongue	Retracts tongue
Palatoglossus	Extrinsic	Palatine aponeurosis	Lateral tongue	Elevates posterior tongue

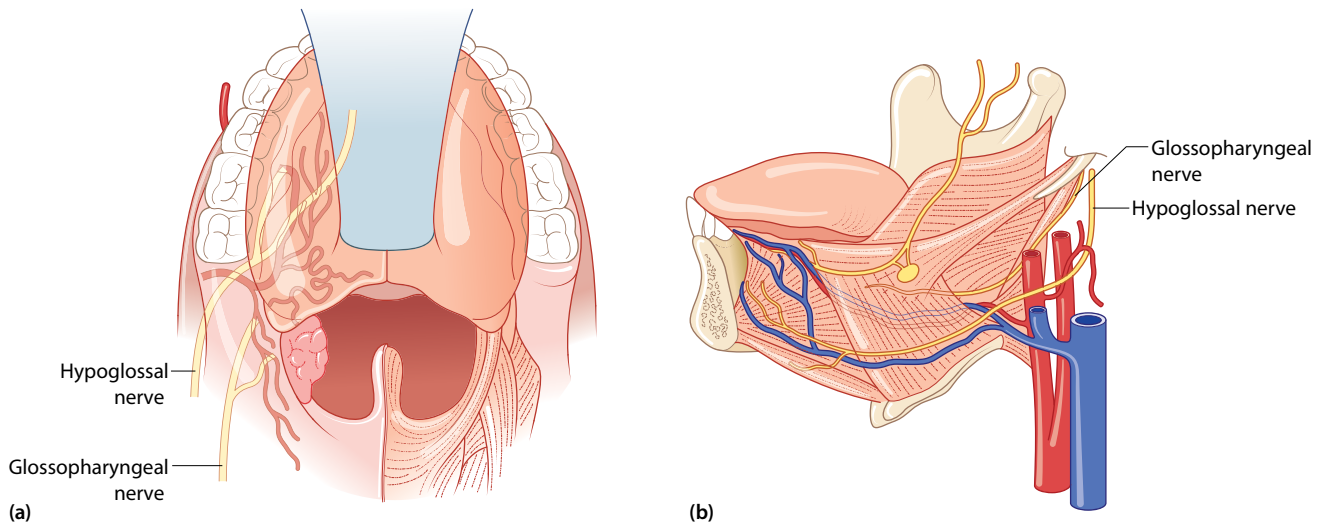

Figure 23.3 Transoral and lateral view of the nerves of the tongue.

Nerves

All the tongue muscles are innervated by the hypoglossal nerve apart from the palatoglossus, which is supplied by the pharyngeal plexus.

The hypoglossal nerve passes through the hypoglossal canal travelling alongside fibres from C1–2, then passing over the internal and external carotid arteries. It is seldom seen during transoral surgery for tongue base pathology (**Figure 23.3a** and **b**). It passes deep to the lingual nerve, along the genioglossus towards the tip of the tongue, and small off-shoots supply the intrinsic and extrinsic muscles apart from palatoglossus.[1]

The glossopharyngeal nerve supplies taste to the posterior 1/3rd of the tongue via the lingual branch. These fibers travel to the inferior glossopharyngeal ganglion and ultimately to the pons/hypothalamus.

Vascular

The principal artery encountered during transoral surgery of the tongue base is the dorsal lingual artery which arises from the common lingual artery. The common lingual artery is usually a branch of the external carotid artery (78%) but in 20% of cases it may arise from a common lingo-facial artery trunk.[2]

The artery has been divided into four segments by Shangkuan et al,[2] the original segment, the segment within the hyoglossus, the ascending and the horizontal segments (**Figure 23.4**).

The original segment consists of the root of the lingual artery which ascends medially then descends anteriorly, it consistently lies 3 to 4 mm supero-lateral to the greater horn of the hyoid bone. This artery is encountered when skeletonizing the greater horn of the hyoid bone deep to hyoglossus muscle.

The segment within the hyoglossus passes obliquely from posterosuperiorly to anteroinferiorly under the posterior border of the hyoglossus muscle and medial to the hypoglossal nerve; prior to entering the intrinsic muscles of the tongue, it runs lateral to the genioglossus.[1] The dorsal lingual artery, the first branch of the lingual artery arises approximately 0.7 cm from the anterior border of the hyoglossus. The vascular territory of the dorsal lingual artery stretches from the root of tongue, 5 mm behind the terminal sulcus, to the glossoepiglottic folds, the glossopalatine arch and the epiglottis.

The ascending segment of the lingual artery ascends in a tortuous manner along the anterior border of hyoglossus. The sublingual artery arises 0.8 cm above the hyoid bone at the origin of the ascending segment passing forward between genioglossus and the sublingual gland. The vascular territory of the sublingual artery includes the ventral side of the tongue, the anterior and lateral floor of the mouth and the vestibular and lingual gum.

The horizontal segment of the lingual artery becomes the deep lingual artery which runs forward with many upward and downward tortuosities between the longitudinal muscle of tongue and the genioglossus of each side, extending to 1cm from the tip of the tongue. The vascular distribution includes the dorsal side of the tongue, the lateral side and part of the ventral side.[3]

VASCULATURE ENCOUNTERED DURING SURGERY FOR TONGUE BASE TUMOURS

The position of the lingual artery within the tongue base is 2.7 cm inferior and 1.6 cm lateral to the foramen cecum (**Figure 23.5**). Dissection within the intrinsic muscles of the tongue tends to be safe, the main trunk lies on the lateral surface of the genioglossus muscle.[4] Intra operative and post-operative bleeding can be controlled with electrocautery or haemostatic clips. More severe bleeding may require transcervical ligation of the lingual and facial arteries.[5]

The veins of the tongue mirror the arteries in name and in their passage through the tongue.

LATERAL PHARYNGEAL WALL

The pharynx is a musculomembranous tube shaped like an inverted cone. It extends from the cranial base to the lower border of the cricoid cartilage, where it becomes continuous with the oesophagus.

Muscles

The muscles of the pharynx are three circular constrictors and three longitudinal elevators. The constrictors may be thought of as three overlapping cones which arise from

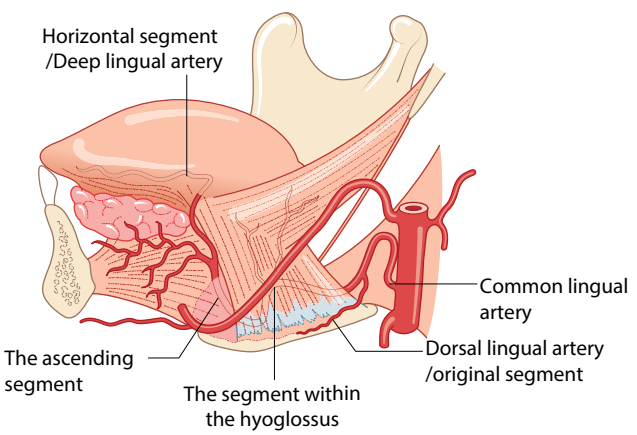

Figure 23.4 Blood vessels of the tongue.

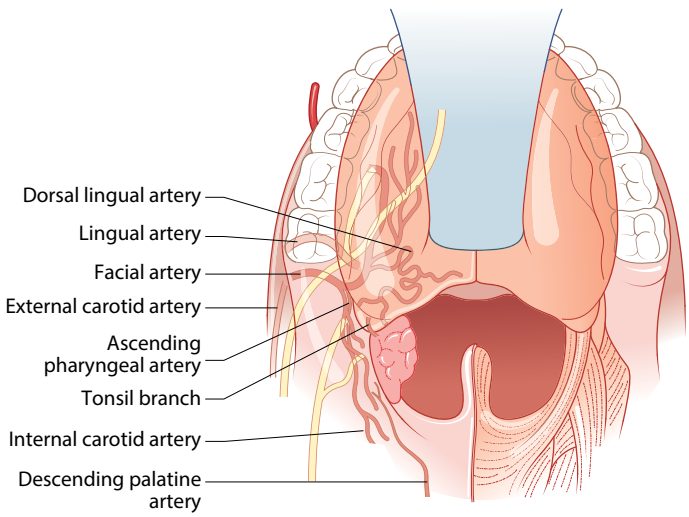

Figure 23.5 Transoral view of the blood vessels of the tongue.

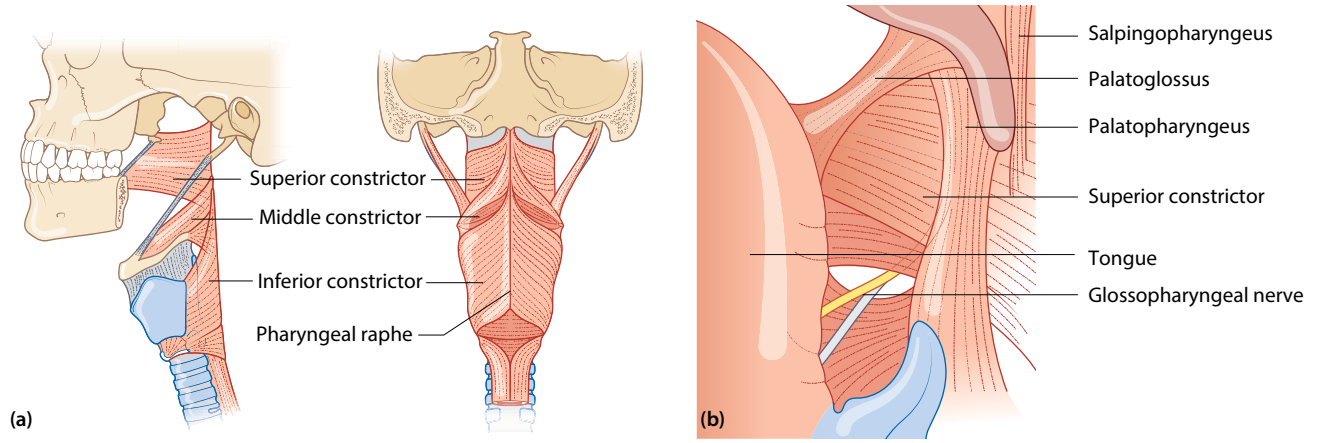

Figure 23.6 **(a)** Pharyngeal constrictors **(b)** Anatomy of the Superior lateral pharyngeal wall.

structures at the sides of the head and neck and pass posteriorly to insert into a midline fibrous band, the pharyngeal raphe (**Figure 23.6a**).

The tonsil is the most medial structure of the lateral pharyngeal wall. It lies between the palatoglossus (anterior faucial pillar) and palatopharyngeus (posterior faucial pillar) muscles. Superiorly these muscles unite with the levator and tensor palatine muscles; inferiorly they are attached to the tongue and pharyngeal wall respectively merging with the superior constrictor.

Deep to the tonsil lies the first of the circular constrictor muscles, the superior constrictor, which originates from the posterior midline pharyngeal raphe and attaches to the pterygomandibular raphe. The constrictors (superior, middle and inferior) overlap each other and all attach to the pharyngeal raphe posteriorly. They act in unison to propel the food bolus into the oesophagus by contracting the lumen.

Continuing to move laterally through the neck the two muscles encountered are styloglossus and stylopharyngeus (**Figure 23.6b**). The styloglossus, an extrinsic tongue muscle, is located superior-anteriorly compared to the stylopharyngeus. These are longitudinal muscles that shorten and widen the pharynx, and elevate the larynx during swallowing.

Nerves

The pharyngeal plexus is responsible for the majority of the innervation of the pharynx. The pharyngeal plexus is comprised of branches of; the glossopharyngeal nerve (CN IX), the vagus nerve (CN X) and sympathetic fibres of the superior cervical ganglion.

The sensory supply to the oropharynx is via the glossopharyngeal nerve (CN IX) and the laryngopharynx is supplied by the vagus nerve (CN X). The glossopharyngeal nerve is located between the styloglossus and stylopharyngeus which in turn lie between the superior and middle constrictors. The glossopharyngeal nerve is consistently identified at the junction of the posterior tonsillar pillar and the tongue base.

The motor supply for all the muscles of the pharynx is the vagus nerve except for stylopharyngeus, which is innervated by the glossopharyngeal nerve.

Vascular

The vascular supply for the lateral pharyngeal wall originates from the external carotid. The upper part of the pharynx receives blood from the pharyngeal branch of the ascending pharyngeal artery and descending branches of the lesser palatine arteries. The lower part of the pharynx is supplied from inferior thyroid artery and superior thyroid artery. The rest of the pharynx receives blood from the ascending palatine and tonsillar branches of the facial artery as well as from the maxillary artery (**Figure 23.7**).

The vascular supply to the tonsil is via tonsillar branches of the ascending pharyngeal and facial arteries, occasionally there may also be a branch from the lingual artery. The tonsillar vessels are commonly found on the medial surface and running through the superior constrictor.

Vasculature encountered during surgery for tonsil tumours

The space between the stylopharyngeus muscle and the superior constrictor muscle contains an irregular and complex venous network called the pterygoid venous plexus, which is partly hidden behind the belly of the stylopharyngeus muscle. Beyond the pharyngeal plexus antero-medially along the superior constrictor the ascending pharyngeal artery and the ascending palatine artery, a branch of the facial artery can all be visualized. The facial, lingual and ascending pharyngeal branches of the external carotid artery lie approximately 5–8 mm deep to the styloglossus.[6,8]

Venous drainage of the superior aspect of the pharynx is via the retromandibular and facial veins which drain into the internal jugular vein. The inferior aspect of the pharynx venous drainage is through the pharyngeal plexus. The pharyngeal plexus can drain either into the internal jugular vein or brachiocephalic vein via the inferior thyroid vein (**Figure 23.8**).

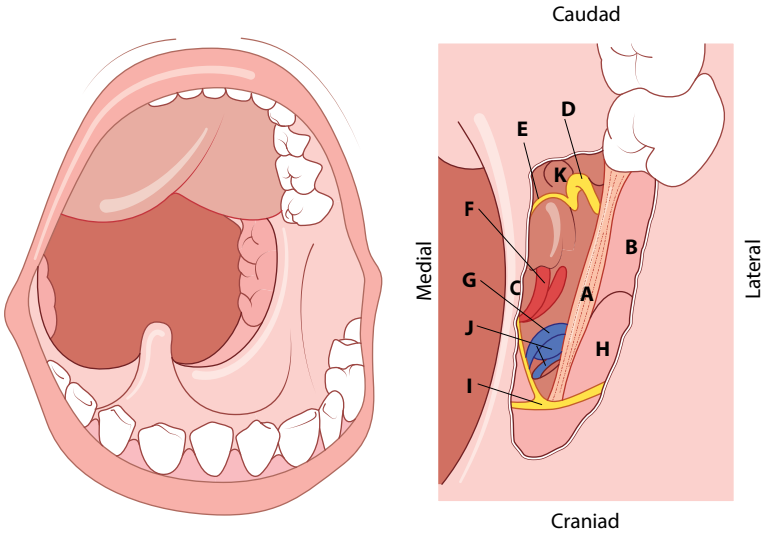

Figure 23.7 Transoral view of the right tonsillar fossa. A, Styloglossus muscle, B, medial pterygoid muscle, C, palatoglossus muscle, D, lingual artery, E, tonsillar branch of the lingual artery, F, tonsillar branch of facial artery, G, tonsillar branch of ascending pharyngeal artery (middle pharyngeal branch), H, superior constrictor muscle, I, tonsillar branch of descending palatine artery, J, tonsillar venous plexus, and K, submandibular gland.

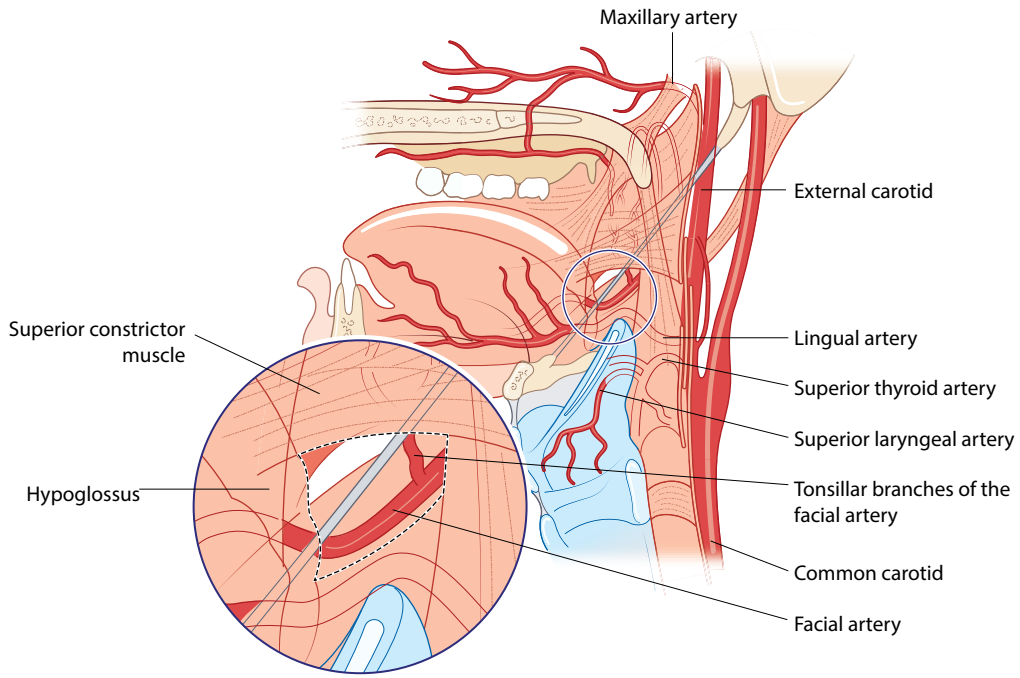

Figure 23.8 The arterial supply to the oropharynx from the external carotid artery.

LARYNX

The main laryngeal framework is composed of the hyoid bone, the thyroid cartilage; a fusion of two quadrilateral shaped laminae, and the cricoid cartilage (**Figure 23.9**). The larynx is suspended from the hyoid bone by two membranes (also termed ligaments), the medial and lateral thyrohyoid membranes.[1]

Cartilages

The thyroid cartilage attaches anteriorly to the cricoid cartilage through the cricothyroid membrane and posteriorly through the cartilaginous cricothyroid joints. Inferiorly the lower border of the cricoid cartilage is attached to the trachea by the cricotracheal ligament. The medial and lateral thyrohyoid membranes along with the cricotracheal

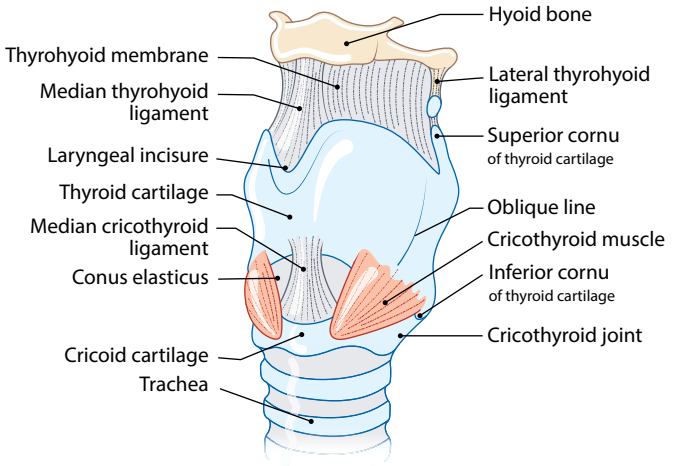

Figure 23.9 A topographical over view of the larynx.

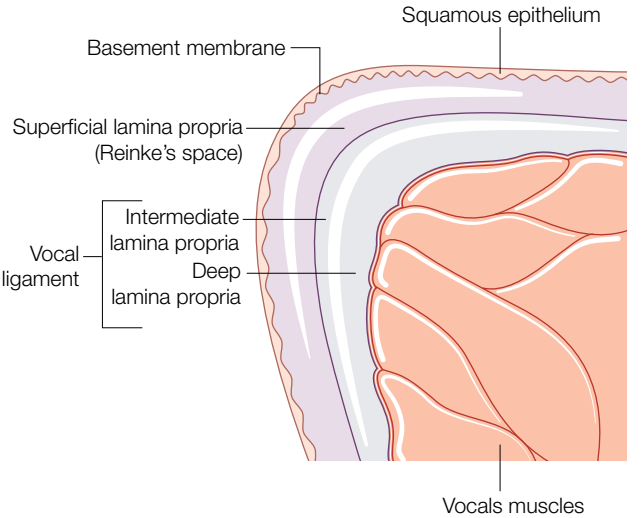

Figure 23.10 The superficial and deep layers of the true vocal cords

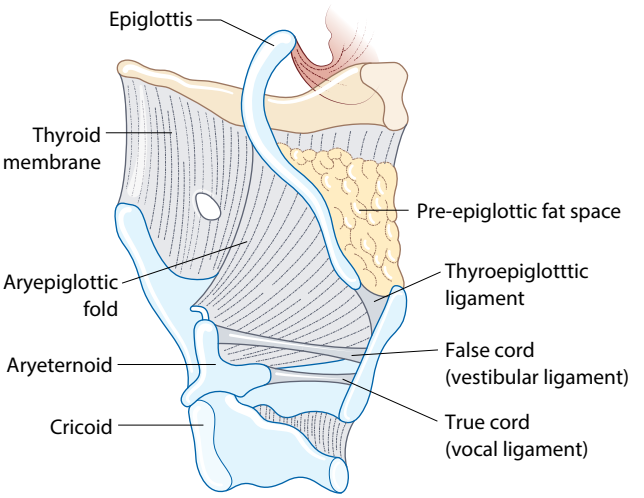

Figure 23.11 Schematic diagram of the larynx in the sagittal plane demonstrating the pre-epiglottic space.

membrane are termed extrinsic ligaments of the larynx. Within the thyroid cartilage, the endolarynx is supported by intrinsic ligaments which lie beneath the laryngeal mucosal membrane forming an internal framework and connecting the internal laryngeal cartilages together.[2] There are two intrinsic fibro-elastic membranes divided by the laryngeal ventricle; the quadrangular membrane, stretching from the arytenoid cartilage to the epiglottis, the free superior border being named the aryepiglottic fold, and the inferior free border forming the ventricular or false vocal fold. The inferior membrane, called conus elasticus, has attachments below to the upper border of the cricoid cartilage, to the mid-point of the thyroid prominence of the thyroid cartilage anteriorly and the vocal process of the arytenoid posteriorly. The free superior edge of the conus elasticus forms the true vocal ligament.

The true vocal cords extend from the angle of the thyroid cartilage to the vocal processes of the arytenoid cartilages. The vocal cords are layered structures with a surface layer of non-keratinizing, stratified squamous epithelium (**Figure 23.10**).

The fusion of the two vocal cords anteriorly produces the anterior commissure tendon. The anterior commissure is an important area for transoral surgery as the epithelium reaches within 1 to 2 mm of the cartilage, there is no perichondrium at this site, and it is a difficult area to expose during surgery. Superior to the anterior commissure the thyroepiglottic ligament attaches the epiglottis to the thyroid cartilage. The epiglottic cartilage extends superiorly and posteriorly forming an important anatomical space within the larynx, the pre-epiglottic space. The pre-epiglottic space is bounded anteriorly by the thyrohyoid ligament, the hyoid bone, and posteriorly by the epiglottis, and superiorly by the hyoepiglottic ligament, connecting the epiglottis to the hyoid bone (**Figure 23.9**).

Posteriorly the vocal cords attach to the vocal process of the arytenoid cartilages (see **Figure 23.11**). The arytenoid cartilages are pyramidal in shape, having a forward projection already mentioned, the vocal process, and a lateral projection, the muscular process to which the posterior cricoarytenoid and lateral cricothyroid muscles attach. These paired cricoarytenoid units are the main functional elements of the larynx involved in speech and swallowing and thus at least one unit must be preserved if meaningful laryngeal function is to be maintained. Two corniculate cartilages articulate with the apices of the arytenoid cartilages. Within the aryepiglottic folds sit two small cuneiform cartilages.

Between the vocal and vestibular ligaments there is a horizontal slit which opens into a recess, the laryngeal ventricle. A diverticulum of the laryngeal ventricle termed the laryngeal saccule extends vertically between the vestibular ligament and the thyroid cartilage. The saccule contains numerous mucous secreting glands to keep the vocal cords lubricated.

The vestibular folds are thick mucus membranes enclosing the vestibular ligament; this being the lower border of the quadrilateral membrane, the superior edge being the aryepiglottic fold (**Figure 23.12**).

Another important anatomical space in laryngeal oncological surgery is the paraglottic space which lies laterally to the conus elasticus and medial to the thyroid cartilage, having the pyriform sinus mucosa as a posterior border (**Figure 23.13**).

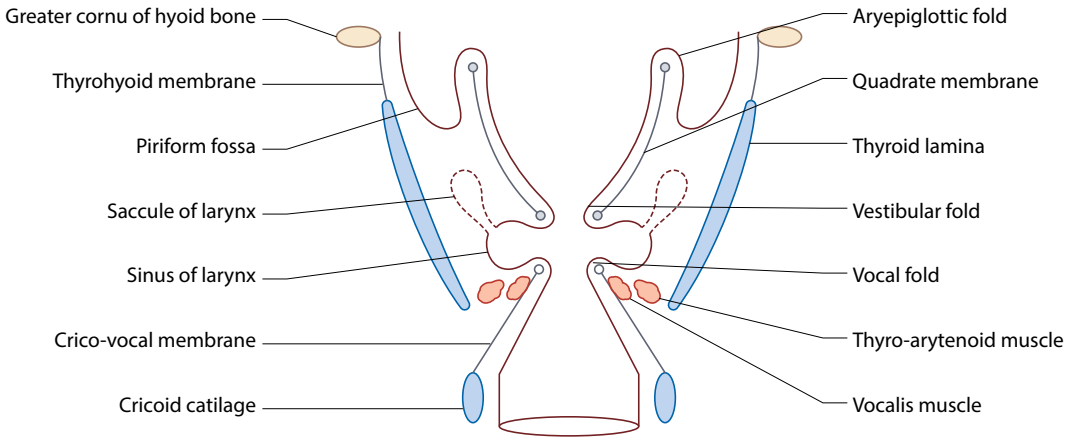

Figure 23.12 Schematic illustration of the endolarynx with the intrinsic membranes, the vestibules and the saccules.

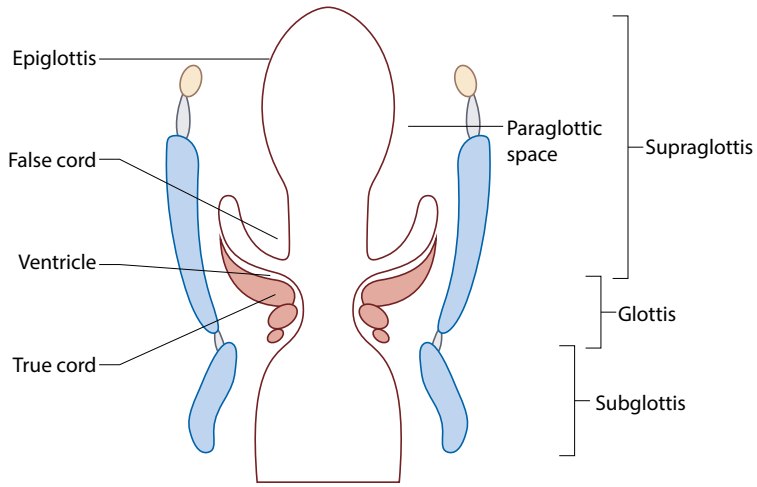

Figure 23.13 Schematic diagram of the larynx demonstrating the paraglottic spaces.

Muscular

The internal laryngeal muscles move the laryngeal cartilages relative to one another, affecting tension and position of the true vocal cords. The thyroarytenoid muscle is a broad flat muscle lying deep to the free edge of the vocal ligament, originating from the thyroid prominence and cricothyroid ligament and inserting in to the vocal process and anterolateral surface of the arytenoid cartilage. The medial portion of the thyroarytenoid muscle is termed the vocalis muscle. The extrinsic portion of the thyroarytenoid muscle inserts anteriorly in to the anterior commissure as thick fibrous tissue known as Broyle's ligament. The intrinsic muscles of the larynx are depicted in **Figure 23.14**.

Vascular

The blood supply to the larynx is derived from the superior and inferior thyroid arteries. The superior laryngeal artery (a branch of the superior thyroid artery) is the artery of main concern regarding post-operative bleeding in TLM / TORS. The superior laryngeal artery courses deep to the thyrohyoid muscle and pierces the thyrohyoid membrane along with the internal branch of the superior laryngeal nerve to enter the larynx.

RELEVANT VASCULATURE ENCOUNTERED DURING SURGERY FOR SUPRAGLOTTIC TUMOURS:

The pharyngoepiglottic fold is important in transoral surgery due to the presence of the neurovascular bundle, comprised of the superior laryngeal artery, superior laryngeal vein and the internal branch of the superior laryngeal nerve (**Figure 23.15**).[3] The artery travels within the pharyngoepiglottic fold to then divide in to five branches:[4] an ascending branch supplies the epiglottis which anastomoses with branches from the lingual artery within the vallecular,[5] other branches supply the ventricle, post-cricoid region, false vocal cords and the thyroarytenoid muscle (**Figure 23.16**). There is a consistent branch of the superior laryngeal artery which runs from posterior to anterior within the undersurface of the false cord. The superior laryngeal artery can generally be found in the superior portion of a triangle formed by the anterior commissure, the vocal process of the arytenoid cartilage, and the attachment of the aryepiglottic fold to the epiglottis.[6,7] Variations of the anatomy of the superior laryngeal artery course exist with a potential for this named vessel being found within the paraglottic space.

The inferior laryngeal artery arises from the inferior thyroid artery and courses with the recurrent laryngeal nerve on the trachea, entering the larynx beneath the

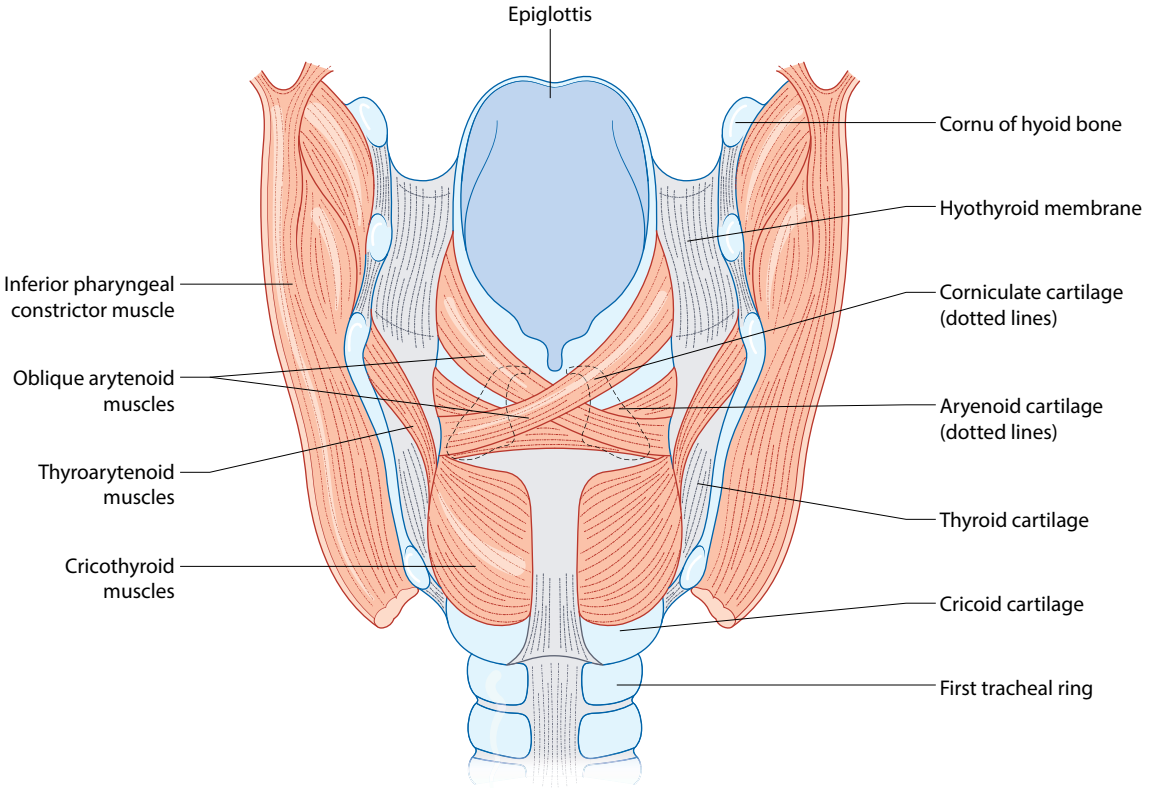

Figure 23.14 A posterior view of the larynx showing the intrinsic muscles of the larynx.

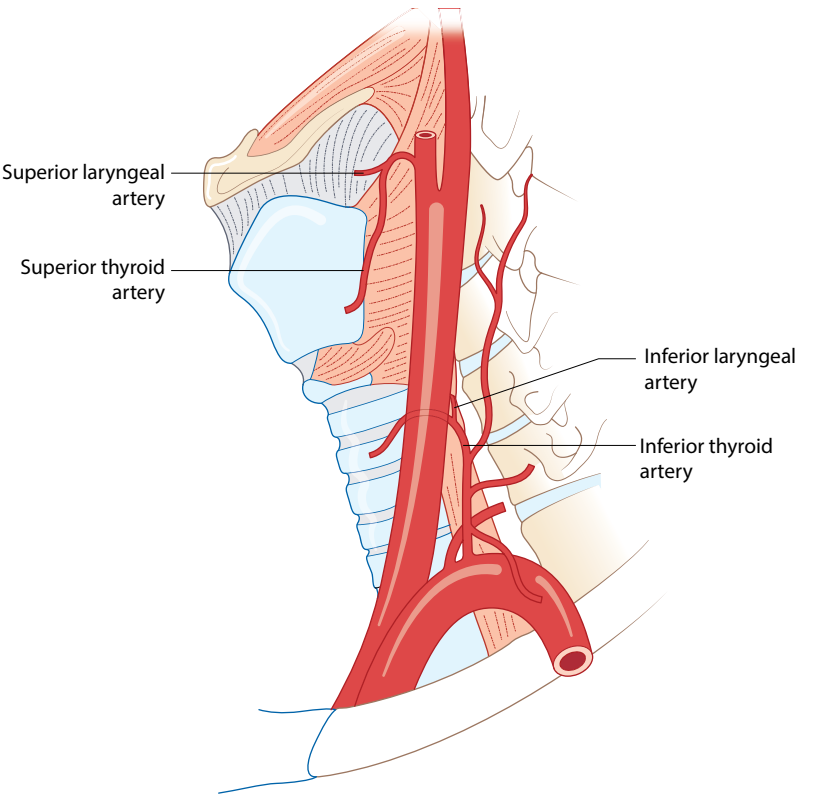

Figure 23.15 The origin and course of the superior laryngeal artery.

lower border of the inferior constrictor. The cricothyroid artery is a branch of the superior thyroid artery and passes across the upper part of the cricothyroid ligament.

Neurological

The motor and sensory supply to the larynx is derived from the vagus nerve. At the level of the greater cornu of the hyoid bone, the superior laryngeal nerve divides in to internal and external laryngeal nerves. The internal branch pierces the thyrohyoid membrane just above where the superior laryngeal artery enters the membrane. The internal laryngeal nerve gives sensory and secretomotor supply to the larynx above the level of the vocal cords (**Figure 23.17**). The branch terminates by piercing the inferior constrictor and uniting with an ascending branch of the recurrent laryngeal nerve; this anastomosis is termed Galen's anastomosis. The internal branch of the superior laryngeal nerve is intimately associated with the superior laryngeal artery and this is an important consideration in oncological resection. This nerve generally splits in to two branches; one which supplies the mucosa above the ventricle and one which supplies the mucosa below the ventricle.[7] If the mucosa superiorly is to be removed as in excision of a supraglottic lesion then preservation of the superior branch is irrelevant. Preservation of the inferior branch which supplies the mucosa below the vestibule along with the hypopharynx could potentially help with the cough reflex preventing aspiration.

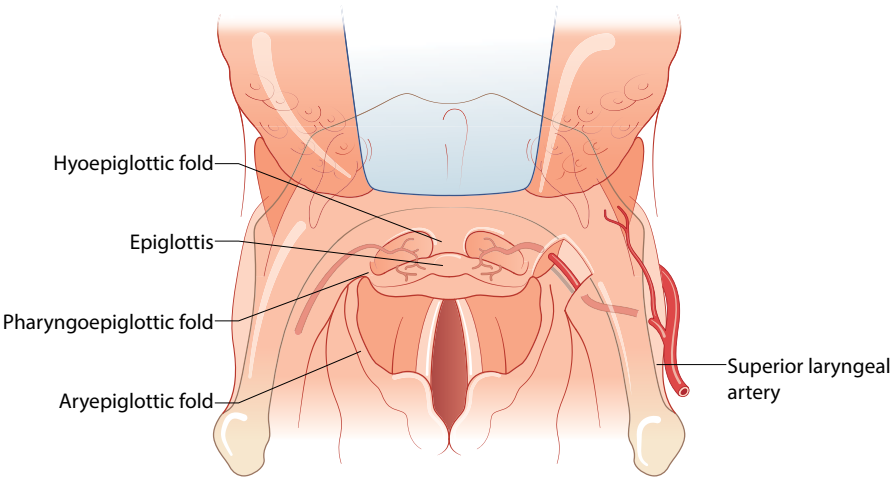

Figure 23.16 The course of the superior laryngeal artery.

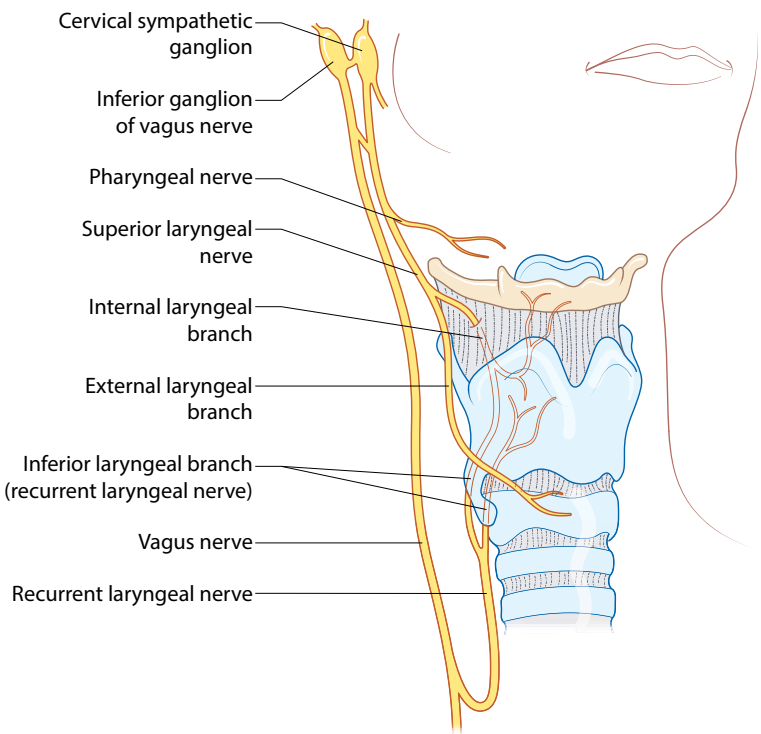

Figure 23.17 The course of the recurrent laryngeal nerve and the superior laryngeal nerve.

KEY POINTS

- A detailed knowledge of the oropharynx, hypopharynx and larynx is essential for all head and neck surgeons.
- The complexities of trans oral surgery turns the conventional anatomy 'inside out', this alternative viewpoint needs to be appreciated before embarking on transoral surgery.

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CHAPTER 24

PRINCIPLES OF CHEMOTHERAPY

Charles G. Kelly

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SEARCH STRATEGY

Data in this chapter may be updated by a PubMed search using the keywords: chemotherapy, induction chemotherapy, concurrent chemotherapy, radiosensitizers, targeted biological agents, recurrent head and neck cancer, metastatic head and neck cancer and EXTREME trial.

INTRODUCTION

Chemotherapy alone cannot cure head and neck cancer. It is used in conjunction with other treatments, surgery and radiotherapy, to improve outcomes such as better local control, organ preservation with continued organ function and decrease the incidence of subclinical micrometastatic spread. Chemotherapy is given for its direct tumouricidal effect, at both the local primary and distant metastatic sites. If given with radiotherapy it can have a radio-sensitizing effect, making cancer cells more susceptible to radiotherapy and increasing the cancer cell kill.

If the cancer has already caused organ destruction and there is no future option to maintain organ function, then surgery with or without adjuvant radiotherapy may give the best chance of cure and long-term survival. Organ preservation is pointless if the patient is left with a non-functioning organ, especially if it may lead to future problems such as aspiration. Chemotherapy can be used in this situation as well. It may be used as induction chemotherapy to shrink the advanced primary tumour or shrink and render fixed cervical nodes mobile, potentially enabling technically easier surgery.

In locally advanced head and neck cancer, chemotherapy can be used at different points in the patient pathway. Chemotherapy is not given routinely for early primary T1/T2 disease, without nodal involvement. It can be used as induction or neoadjuvant treatment before the primary treatment, be that surgery or radiotherapy; but if used for induction this is almost always before radiotherapy rather than surgery as its use would inevitably delay surgery. However, the preparatory processes before radiation therapy, such as manufacturing an immobilization device and creating a radiotherapy plan, consume time and these can take place while the patient is having induction chemotherapy, thereby bringing forward the initial treatment start date.

If induction chemotherapy is used, further chemotherapy is usually given with subsequent radiotherapy, and this is known as concomitant chemotherapy, which is more commonly used; only a minority of patients receive induction regimens.

Adjuvant chemotherapy, which is treatment given after the principal treatment, is not used as a sole modality after radiotherapy, as it has not been shown to have benefit in this setting; however, when given with adjuvant radiation, it has been shown to improve local control and increase survival where primary surgery has been the definitive treatment. This benefit is seen in patients who have a higher risk of recurrence with positive surgical margins, nodal involvement, especially multiple nodes involved or extra capsular spread.

CHEMOTHERAPY AND HPV-POSITIVE TUMOURS

Human papillomavirus (HPV) is known to have an aetiological role in introducing head and neck cancers, especially in the oropharynx where HPV infection may be linked to 50–80% of tumours. There is also some growing evidence for HPV associated non-oropharyngeal tumours.[1] HPV-positive and -negative head and neck cancers are thought to represent distinct diseases with differing natural histories and prognosis. There is evidence from several studies, for example RTOG 0129, that outcomes are better following treatment in patients with HPV-positive tumours.[2] However, much of this evidence is retrospective, with completed trials being re-interrogated for patients' HPV status, often without complete data being available for all patients entered into these trials. As prospective evidence builds, HPV-positive patients do appear to have better outcomes following treatment when compared to HPV-negative patients. There is also growing evidence that continuing to smoke negates the benefit of the better prognosis given by HPV positivity.

Despite this growing evidence that HPV-positive patients have better outcomes, at present there are not enough robust data to alter chemotherapy or indeed radiotherapy treatment regimens depending on the patient's HPV status, outside of the context of a clinical trial.

There is considerable interest in reducing treatment for patients with HPV-positive tumours and multiple trials are underway worldwide addressing this question.[3–5]

INDUCTION (NEOADJUVANT) CHEMOTHERAPY

As interest in organ function preservation grew, induction chemotherapy was considered to have the potential for several benefits.

If induction chemotherapy could shrink primary tumour volumes before the principal treatment of radiotherapy or chemoradiotherapy, this might allow better blood flow into the tumour allowing a greater tumouricidal dose of drugs to be delivered and decrease the volume of hypoxic areas, which would decrease the radioresistance that hypoxic cancer cells show. If induction chemotherapy could improve local control, there would be a greater chance of functional organ preservation. Since surgery and radiotherapy are both locoregional treatments, induction chemotherapy could theoretically treat distant subclinical metastatic disease.

The response to neoadjuvant chemotherapy could give important prognostic information, as it can act as a surrogate marker for response to later treatment. This latter advantage was used in one of the earliest trials of neoadjuvant chemotherapy for organ preservation, the Veterans trial, in which the patients were given two cycles of cisplatin and 5-fluorouracil followed by response assessment; if there was a response to chemotherapy, patients went on to have chemotherapy and radiotherapy but if there was no response, the patients went directly to laryngectomy.[6]

Most patients who have had induction chemotherapy go on to have concurrent chemotherapy as well. There is a risk that patients undergoing induction chemotherapy may be more at risk of not completing or having breaks in the subsequent definitive radiotherapy treatment because of the morbidity induced by induction chemotherapy, which would result in poorer outcomes.

One of the main evidence sources for the use of chemotherapy in head and neck cancer is the meta-analysis of chemotherapy in head and neck cancer (MACH-NC), which was originally published in 2000 and updated in 2007 and 2009.[7–9] These overviews reviewed more than 90 trials containing data on more than 16 000 patients, with overall survival as the primary endpoint. The analysis failed to show an overall survival benefit from the use of induction chemotherapy when compared to primary surgery or radiotherapy alone, although cisplatin and 5-fluorouracil (5-FU) as a combination did show some benefit. However, these reviews did suggest that induction chemotherapy may reduce the incidence of distance metastases, more effectively than concurrent chemotherapy.

There is still debate as to whether induction chemotherapy followed by concurrent chemoradiotherapy is more beneficial than concurrent chemoradiotherapy alone. Some large trials have shown no benefit[10] while others have shown some.[11] Interest was rekindled in induction chemotherapy when two trials, one European and one from North America, 'TAX 323' and 'TAX 324' showed benefit by including a taxane, such as docetaxel or paclitaxel in the induction chemotherapy regime in addition to cisplatin and 5-FU.[12, 13] Response rates and survival outcomes were higher with taxane-containing regimens but toxicity was considerably higher and chemotherapy-related deaths were also increased with these regimens. Such sequential regimens are offered to patients with good performance status and fewer comorbidities, and those with bulky nodal disease, stage N2b and above, and where surgery is not appropriate.

CHEMOTHERAPY REGIMENS USED IN INDUCTION CHEMOTHERAPY

The standard regimen was formerly cisplatin 100 mg/m² and 5-fluorouracil, 1 g/m² per day for 4–5 days via a chemotherapy infusion bottle. This was given 3-weekly for two to three cycles, before definitive treatment. The definitive treatment is almost always concurrent chemoradiotherapy, except in a few cases where induction chemotherapy can be used in the hope of converting inoperable locoregional disease to more surgically manageable disease.

The European TAX 323 and the North American-based TAX 324 trials[12, 13] produced evidence that adding a taxane, such as docetaxel or paclitaxel to cisplatin and 5-FU (i.e. TPF vs PF) did improve survival in the TPF arm, but at a cost of much higher toxicity, both

haematological with myelosuppression and neutropenia and non-haematological, especially increasing mucositis.

In TAX 323, no concurrent chemotherapy was given with subsequent radiotherapy and in TAX 324, concurrent carboplatin was used. This has led to some criticism that the most optimal concurrent chemotherapy available was not given in the studies. The TPF doses were also different in each of these trials. Both studies did show TPF gave better overall survival than cisplatin and 5-FU alone.

The most effective, optimal and least toxic sequential chemotherapy regimen is still debated and more recent publications have been less encouraging. The TREMPLIN study by Lefebvre et al[14] used induction chemotherapy followed by chemoradiotherapy or by cetuximab plus radiotherapy. There was no difference in outcome with regard to larynx preservation. The PARADIGM trial,[15] which compared sequential chemotherapy versus concomitant chemotherapy alone, showed no overall survival difference in locally advanced head and neck cancer. The DeCIDE trial[16] also found no overall survival difference in patients with nodal stages N2/N3 disease, where induction chemotherapy was added to concomitant chemo-radiotherapy compared with concomitant chemotherapy alone.

These disappointing induction trials are reviewed by Garden[17] in an editorial suggesting that the evidence to date does not suggest that induction chemotherapy is beneficial in head and neck cancer.

CONCURRENT OR CONCOMITANT CHEMOTHERAPY

Concurrent or concomitant chemotherapy given with radiotherapy is more frequently used than induction or sequential chemotherapy. It is given for its direct cell-killing effect and for its effect in sensitizing cancer cells to the effects of radiotherapy. It probably has less effect in suppressing micro-metastatic distant spread than induction chemotherapy. Its main advantage is that when used with radiotherapy, without induction chemotherapy, there is less chance of patients having to stop treatment because of toxicity, and have breaks in radiotherapy, which can be detrimental to treatment outcome.

In the meta-analysis of chemotherapy on head and neck cancer (MACH-NC),[7–9] the overview looked at concurrent chemotherapy in 16 000 patients and showed that it gave a survival benefit when added to radiotherapy alone, giving a 6.5% decrease in mortality at 5 years, in absolute terms. This benefit was not seen in patients over 70 years of age, but patients over 70, formed a very small number of the total patients reviewed.

The most commonly use concurrent chemotherapy regimens are cisplatin 100 mg/m² at days 1, 22 and 43 of radiotherapy, either alone or with 5-FU, 1 g per day on days 1 to 4. Although this regimen is commonly used, there are few direct comparisons with other concomitant chemotherapies within randomized controlled trials.

Increased toxicity produced by adding platinum chemotherapy to radiotherapy can be considerable with more marked mucositis, dysphagia, nephrotoxicity, ototoxicity, myelodysplasia and neutropenia. A significant proportion of patients do not receive all three cycles of chemotherapy because of toxicity, but one study has shown no survival difference in patients receiving two cycles of cisplatin rather than three cycles; however, the radiotherapy delivered was not identical within the arms of this study.[18] Chemotherapy toxicity can also interfere detrimentally with radiotherapy delivery causing breaks and treatment which are associated with poorer outcomes.

While high-dose cisplatin, 100 mg/m², 3-weekly may be optimal for younger patients with good performance status and fewer comorbidities, many head and neck patients are not in this category and other dose regimens may be better tolerated. Cisplatin, 40 mg/m², capped at a total of 70 mg given weekly, may allow for more flexibility with the ability to reduce or omit a weekly dose in response to changes in the patient's tolerability and individual toxicity. Daily cisplatin at a dose of 6 mg/m² is also an occasionally used regimen. Weekly and daily regimens may be easier to administer in an outpatient or day ward setting. High-dose cisplatin at 100 mg/m² may require inpatient admission for prehydration and monitoring.

If cisplatin is contraindicated because of renal function status, the presence of neuropathy, tinnitus or deafness, or where there is a danger of fluid overload with the necessary pre-hydration used in cisplatin administration, carboplatin can be considered as it causes less nephrotoxicity, ototoxicity and peripheral neuropathy but is more myelosuppressive. It is not thought to be as tumouricidal as cisplatin and for this reason it has now been largely overtaken by the epidermal growth factor receptor (EGFR) inhibitor, cetuximab in clinical practice when cisplatin is contraindicated.

CONCURRENT RADIOSENSITIZERS

It is known that tumour cell hypoxia induces radioresistance, and there has been renewed interest in giving hypoxic cell radio-sensitizing drugs during radiotherapy. The two most common in use are the anti-helminthic drug nimorazole, which is extensively used in some parts of Europe, and tirapazamine, an anticoagulant that is activated in hypoxic environments. Although established in some parts of the world, trials are ongoing with these agents to establish efficacy and with nimorazole, patient tolerability.

TARGETED BIOLOGICAL AGENTS

Targeted therapy in head and neck cancer developed with the recognition that EGFR is overexpressed in most head and neck cancers, up to 90% in some studies, and is associated with a poorer prognosis. When a growth factor attaches to its receptor on the cell surface, cells are stimulated to divide and consequently tumours grow. If the receptor is abnormal because of a mutation the stimulation to divide may even occur without growth factors interacting with the receptor. Cetuximab is a

mouse–human chimeric monoclonal antibody that binds to the extracellular portion of EGFR and turns this signalling system off.

In the initial innovative cetuximab trial by Bonner et al,[19] patients with advanced cancers of the oropharynx, larynx or hypopharynx were randomized to receive radical radiotherapy with or without cetuximab. At 3 years, survival was better in the patient group who had received cetuximab, 55% vs 45%; and local control was also better, 50% compared to 41%.[20] Subset analysis, with its inherent limitations, suggested that cetuximab may have more effect in younger patients under 65 years, in those with oropharyngeal cancer and in those with better performance status, broadly reflecting the response with non-targeted standard chemotherapy regimens.

While these initial results with cetuximab were encouraging, a major drawback to the study was that, since it had started, radiotherapy alone as used in this study has been overtaken as a standard of care by chemoradiotherapy for advanced head and neck tumours. Thus, comparing radiation alone versus radiation plus cetuximab is much less relevant in the context of contemporary standard practice.

Despite initial hopes that cetuximab would give less toxicity than standard chemotherapy, and could therefore be given to older patients and those with a poorer performance status, it has been shown to have a different, although not necessarily more gentle toxicity profile. It does show less morbidity with nephrotoxicity, ototoxicity and peripheral neuropathy but it gives patients a more intense grade 3 and grade 4 radiation dermatitis.

Patients may also develop an acne-like rash predominantly over the face, neck and trunk with a more eczema-like condition at the fingertips and elbows, and paronychia may develop. In a minority of patients this reaction can be so severe that cetuximab may need to be stopped but these side effects can usually be managed by increasing the treatment interval and supportive care with topical medications. There is some suggestion that patients who develop this rash also have a better tumour response with improved overall survival.[21]

While receiving cetuximab, infusion-related side effects are not uncommon with headache, flushing, pyrexia, urticaria, swelling of the lips and tongue or bronchospasm. Patients, therefore, usually receive steroids 24 hours before starting a cetuximab infusion. Cetuximab may have a role to play in the treatment of metastatic disease (see below), as shown in the EXTREME trial, but that role is still to be fully defined.

Other targeted EGFR monoclonal antibodies are under investigation, such as panitumumab[22] or zalutumumab,[23] but to date with less encouraging results, showing no improvement in overall survival. Another target further down this biological pathway, offering a different mechanism of action is used by erlotinib, a small molecule inhibitor of EGFR tyrosine kinase. In one phase II trial of erlotinib given alone or combined with cisplatin, unfortunately it did not show any benefit in outcome for the combination. Despite this, other targets in the EGFR pathway are being investigated.[24]

This emerging modality and immuno-oncology are discussed in greater detail in Chapter 30, Biologically targeted agents in head and neck cancers.

CHEMOTHERAPY FOR RECURRENT OR METASTATIC HEAD AND NECK CANCER

Chemotherapy or targeted biological agents may be indicated for patients with recurrent and/or metastatic disease but patients with metastatic disease have a median survival of approximately 6–12 months in most studies.

Appropriateness of chemotherapy depends on several factors, such as: extent and burden of disease; whether symptoms are present or not; and whether failure of control has taken place at the primary site only, there is metastatic disease only, or both. Often, the most important consideration is the fitness and performance status of the patient and whether they could tolerate the proposed chemotherapy, and how much it would reduce their pre-treatment quality of life, for whatever limited survival they have.

LOCOREGIONAL FAILURE

This has been reported in up to 50% of patients with head and neck cancer. Prognosis in this patient group is typically poor and salvage treatments can be limited by the extent of the recurrent disease, the time interval since original treatment and the type of primary treatment.[25]

In this group of patients, if other salvage surgery or re-treatment with radiotherapy and chemoradiotherapy is being considered, it is important to assess the presence of distant metastatic disease, and also to confirm that the locoregional recurrence disease is not a second primary. Discovering that metastatic disease is also present is not an absolute contraindication to salvage treatments at the primary site, as locoregional failure and metastatic disease can be considered as two separate problems in the patient's management plan. If good palliation at the primary site or local regional control can be achieved relatively easily by a salvage procedure, the presence of metastatic disease, especially small volume metastatic disease, should not necessarily stop treatment to the primary or locoregional site. The patients who do better with salvage treatment are those with smaller volumes of recurrence, a longer disease-free interval and fewer comorbidities. Some head and neck subsites, such as the larynx, also have better outcomes than other subsites.[26]

DISTANT METASTASES

Chemotherapy is often indicated here as part of a best supportive care package but has not been shown to significantly extend survival. The presence or absence of symptoms will influence when they receive chemotherapy. The therapeutic window for giving chemotherapy in this

situation would be when the patient still has an appropriate performance status to receive and benefit from chemotherapy, with the trade-off being an improved symptom state for the inevitable morbidity caused by the chemotherapy. Giving chemotherapy to the patient with no symptoms to palliate and little hope of extending survival, while giving some treatment side effects and increased hospital attendances, may well decrease the patient's quality of life by a factor greater than any symptoms alleviated by the chemotherapy. A shared decision-making approach where the patient and his family are given as complete information as possible on the potential benefits and morbidities of having chemotherapy with its likely effect on symptoms, positive or negative effects and prognosis and treatment morbidity may let the patient make a more fully informed decision.

If chemotherapy is to be given for distant metastatic disease, the most appropriate regimen depends on several factors including the performance status, comorbidities present, renal function and the physiological reserve of the patient. Additionally, the regimens the patient has had before and the length of the interval since last chemotherapy was given, may be important.

The most common regimens used are cisplatin or carboplatin with 5-FU. These give an expected response rate of approximately 40%.[27] Carboplatin is used more often in this palliative metastatic setting than with induction or concurrent regimens, because although deemed slightly less effective than cisplatin, it is less toxic and is considered to be more appropriate in the palliative setting.

Elderly patients do appear to respond to platinum-based chemotherapy in the metastatic setting,[28] in contrast to a lack of benefit in the elderly when used in primary chemoradiotherapy regimens. There does, however, appear to be more toxicity using chemotherapy in an elderly patient population than the standard patient population.

Other more toxic chemotherapy regimens have also been investigated using platinum and a taxane (docetaxel or paclitaxel) in combination. These have not been shown to improve survival compared to the standard of care combination of cisplatin and 5-FU, although some studies have found a high response rate but with the cost of higher toxicity.

Cetuximab with cisplatin and 5-FU, which has become a more commonly used regimen, can increase both response rate and improve short-term survival slightly, as shown in the EXTREME trial,[29] but a 5-year follow-up published recently in abstract form shows very low survival for patients in both arms of the study. The EXTREME study did not allow crossover between regimens so similar results might be achieved by the use of cisplatin and 5-FU followed by cetuximab used sequentially. In patients who have become refractory to cisplatin and 5-FU, cetuximab as a single agent does have a low response rate of approximately 10–15%.[30–32]

KEY POINTS

- Concurrent chemoradiotherapy is at present the standard of care for treatment of locally advanced head and neck cancer with a confirmed absolute survival benefit of 6.5% at 5 years.
- Single agent cisplatin, which in the past has been shown to be as effective as multiple drug regimes, is now being challenged by the introduction of the use of taxanes.
- Targeted biological agents, such as cetuximab, have a role to play in both advanced head and neck cancer and recurrent or metastatic disease but those roles are still being established.
- At present HPV status does not alter management regimens, although there are multiple studies underway, examining if less intense treatment, both with radiotherapy and chemotherapy, could be given to achieve the same outcome but with less toxicity.
- The potential benefit of neoadjuvant or induction chemotherapy is being re-examined.
- Elderly patients benefit least in terms of survival advantage with the use of concurrent chemotherapy.

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CHAPTER 25

CYSTS AND TUMOURS OF THE BONY FACIAL SKELETON

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SEARCH STRATEGY

Data in this chapter may be updated by a Medline search using the keywords: odontogenic cyst, jaw cysts, non-odontogenic cysts, and jaw neoplasms.

INTRODUCTION

The maxilla and mandible – the upper and lower jaws, respectively – form an important part of the bony facial skeleton and are unique in that they consist, in part, of the alveolar process which has the sole purpose of supporting the teeth. The teeth develop within the deeper part of the jaws and erupt up through the alveolar process, coming to lie within the tooth socket, suspended by the periodontal ligament which lies between the bony tooth socket and the cementum of the tooth root. The crown of the erupted tooth is cuffed at the neck by gingival mucoperiosteum and this junction of hard and soft tissues is a potential source of infection and inflammation. The inflammation can stimulate odontogenic epithelial remnants left after tooth development leading to the inflammatory radicular cyst, the most common type of cyst affecting the jaws. In addition, other types of odontogenic epithelial residues may give rise to developmental odontogenic cysts. The odontogenic cysts, being unique to the jaws, form a major part of this chapter. Also covered are the non-odontogenic cysts which arise from embryonic epithelial residues found within canals running through the facial bones or entrapped at lines of bone fusion. The non-odontogenic cysts are less common but important in the differential diagnosis of cystic lesions. Non-epithelialized bone cysts are also covered since, although they are rare within the jaws compared to the long bones, they are important in the differential diagnosis of cysts of the facial skeleton.

The second part of the chapter focuses on fibro-osseous lesions, a diverse group of bone conditions that can cause 'tumour' or swelling of the bones, drifting of teeth and radiological appearances that mimic cysts and neoplasms. Some are unique to the jaws and their diagnosis requires detailed clinicopathological correlation. The third part of the chapter deals with 'tumours' ranging from developmental anomalies to true neoplasms beginning with an overview of lesions arising from bone cells. Emphasis is given to the clinical and radiological presentation and any ways in which jaw/facial lesions differ from lesions elsewhere in the skeleton. The odontogenic tumours are covered in detail since they are unique to the jaws and both the diagnosis and management can be challenging. Finally, intraosseous salivary gland tumours, miscellaneous lesions and metastatic tumours are briefly considered.

CYSTS

A simple definition of a cyst is 'a cavity, generally lined by epithelium, filled with fluid or semi solid contents but not formed by the accumulation of pus'. As outlined above and summarized in **Table 25.1**, cysts of the jaws and bony facial skeleton arise from several types of epithelial residues. These residues probably exist within the jaws and covering alveolar/gingival mucoperiosteum in all individuals but the factors which lead to cyst formation are poorly understood.

TABLE 25.1 Classification of cysts of the bony facial skeleton

Lining of cyst lumen	Category of cyst	Subcategory	Source of epithelial lining
Epithelialized	Odontogenic	Developmental and inflammatory (see Table 25.2)	Residues of the tooth-forming organ
Epithelialized	Non-odontogenic	Nasopalatine duct cyst and variants	Remnants of nasopalatine duct (Jacobson's organ)
		Intraosseous dermoid and epidermoid	Entrapped epithelium at lines of embryonic closure
Non-epithelialized	Solitary bone cyst		
	Aneurysmal bone cyst		
	Staphne's idiopathic bone cavity		
	Focal marrow-containing jaw cavity		

TABLE 25.2 Odontogenic epithelial remnants, their origin and associated cyst(s)

Odontogenic epithelial residue	Source of odontogenic epithelial residue	Associated odontogenic cyst(s)
Reduced enamel epithelium	Fusion of inner and outer enamel epithelia of enamel organ	Dentigerous (follicular) and eruption cysts
		Paradental cyst
Rests of Malassez	Root sheath of Hertwig	Radicular (apical and lateral) and residual cysts
Rests (glands) of Serres	Dental lamina	Dental lamina cysts of the newborn (Bohn's nodules)
		Lateral periodontal, botryoid odontogenic cysts and gingival cyst of adults
		Keratocystic odontogenic tumour (formerly, odontogenic keratocyst)

Epithelialized cysts

ODONTOGENIC CYSTS

The odontogenic cysts arise from remnants of the tooth-forming apparatus.[1] There are three distinct types of epithelium which persist once odontogenesis is complete (**Table 25.2**). First, the dental lamina, which, in the developing embryo, is the downgrowth of surface oral epithelium that extends into the underlying developing mesenchymal tissue and gives rise to the enamel organ (**Figure 25.1**). Once tooth formation is complete, this structure fragments, but its persistence as small, rounded islands of epithelium within the bone and alveolar soft tissues, the rests (glands) of Serres, is well recognized (**Figures 25.2–25.4**). These dental lamina residues give rise to the developmental lateral periodontal and gingival cysts (and the keratocystic odontogenic tumour, formerly the odontogenic keratocyst). Second, once enamel formation is complete, prior to eruption, the tooth is covered by a layer of reduced enamel epithelium, formed by fusion of the two layers of inner and outer enamel epithelia. This is the source of epithelium for dentigerous (follicular), eruption and inflammatory paradental cysts. The third epithelial residue is the rests of Malassez within the periodontal ligament between the tooth root and the bony tooth socket which results from the fragmentation of Hertwig's root sheath on the completion of root formation, and gives rise to the inflammatory radicular cysts. The classification of odontogenic cysts used in this chapter (**Table 25.3**) is based on that recommended by the World Health Organisation.[2]

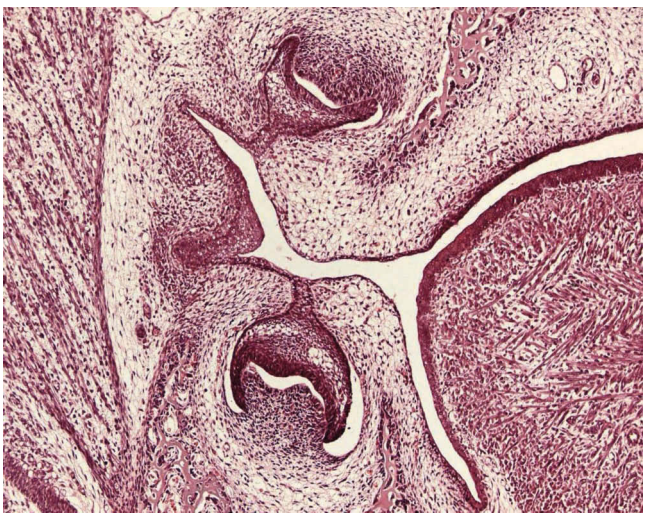

Figure 25.1 Photomicrograph depicting developing tooth germ arising from down growth of oral cavity lining surface epithelium, the dental lamina.

Developmental odontogenic cysts

DENTIGEROUS (FOLLICULAR) AND ERUPTION CYSTS

These account for around 15–18% of jaw cysts. Dentigerous cysts, formed by expansion of the dental follicle, the soft tissue covering the crown of an unerupted tooth, are attached to the cemento-enamel junction. Teeth most commonly affected are those more likely to remain

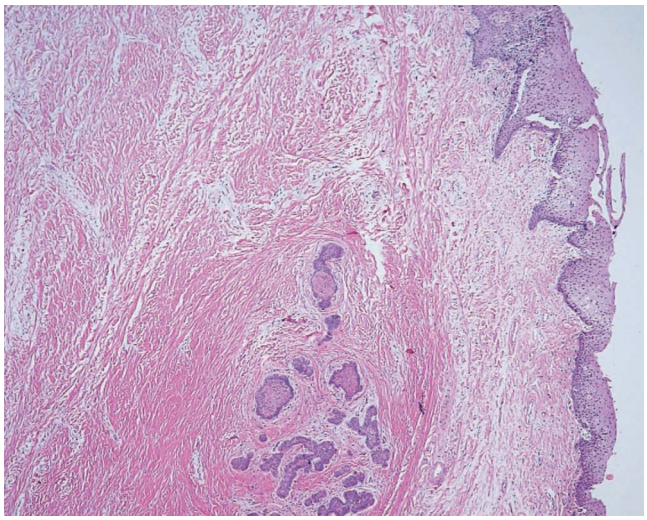

Figure 25.2 Photomicrograph showing remnants of fragmented dental lamina, odontogenic epithelial rests, in an adult within alveolar connective tissues.

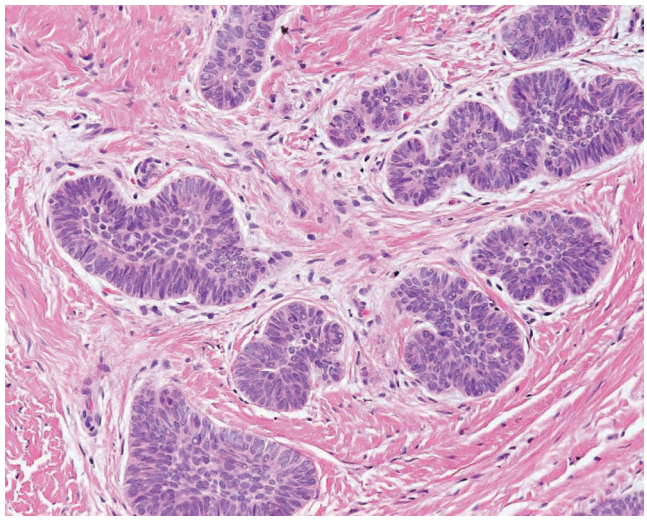

Figure 25.3 Photomicrograph showing remnants of fragmented dental lamina, odontogenic epithelial rests, in an adult within alveolar connective tissues.

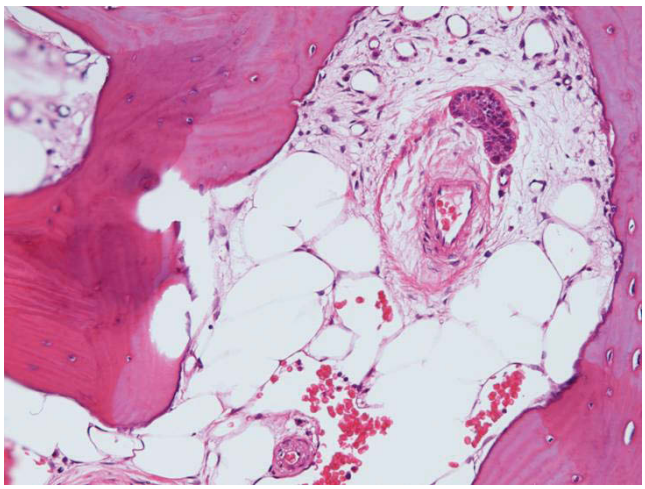

Figure 25.4 Odontogenic epithelial remnants within bone.

unerupted, typically, in order of decreasing frequency, mandibular third molars ('wisdom' teeth), maxillary canines, mandibular second premolars and maxillary third molars. Peak age of presentation is second to third decades but they can be diagnosed later in adulthood. Some present with swelling, displacement of teeth and symptoms resulting from secondary infection but many are found on radiological assessment of a missing tooth. Dentigerous cysts can reach up to 5 cm in radiographic diameter, and the clinical differential diagnosis of larger lesions includes keratocystic odontogenic tumour and unicystic ameloblastoma, two more aggressive lesions that can present in a dentigerous relationship (see below).

Radiographically, dentigerous cysts typically present as unilocular radiolucencies connected to the cemento-enamel junction (**Figures 25.5** and **25.6**). They have a greater tendency than other non-neoplastic cysts to cause root resorption in adjacent teeth[3] possibly because resorption of the deciduous predecessor is a normal function of the follicle.

Histological diagnosis is generally straightforward especially when accurate clinical and radiographic information are provided on the request form. The epithelial lining is thin, either simple cuboidal, columnar or non-keratinized stratified squamous, although metaplasia may result in focal keratinization and scattered mucus and ciliated cells.

TABLE 25.3 Classification of the odontogenic cysts

Pathogenetic category	Cyst type	Subtype	Dental relationship
Developmental	Dentigerous (follicular)	Eruption	Cover the crown of an unerupted tooth; attached to cement-enamel junction
	Lateral periodontal	Gingival cyst of adults	Lateral to root of vital tooth
		Botryoid odontogenic	
	Sialo-odontogenic (glandular odontogenic)		
Inflammatory	Radicular (dental)	Apical	Root apex of non-vital tooth
		Lateral	Lateral root canal of non-vital tooth
		Residual	Within jaw after removal of associated causative tooth
	Paradental		Lateral aspect of partially erupted tooth

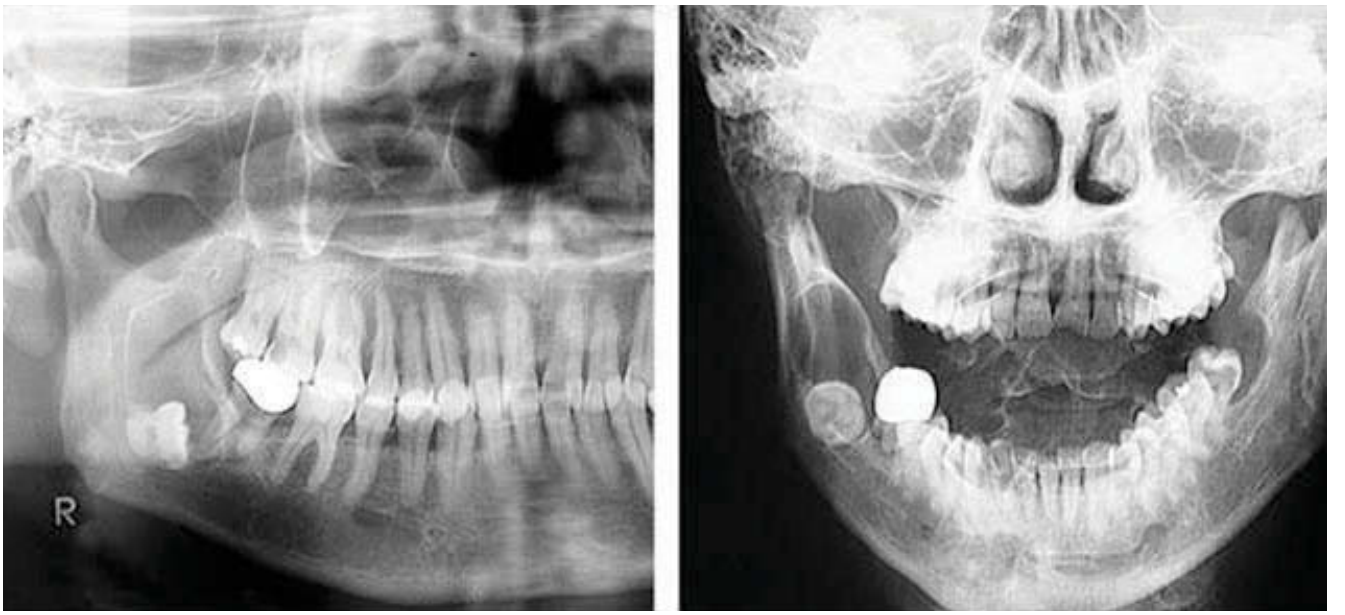

Figure 25.5 Bilateral dentigerous cysts seen radiologically.

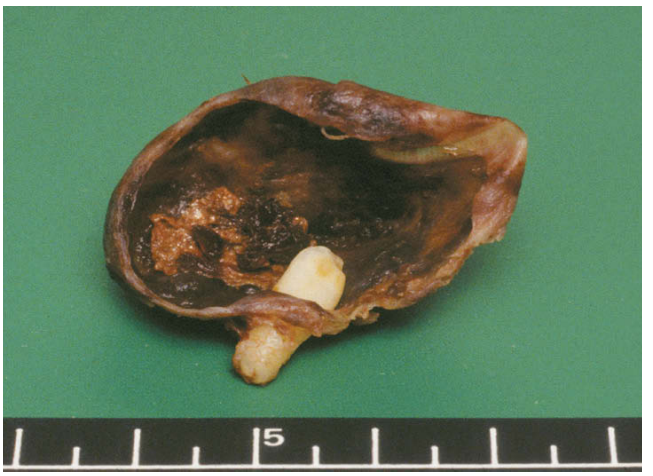

Figure 25.6 Macroscopic image of dentigerous cyst and associated lower premolar (impacted) noting relationship to cemento-enamel junction.

Numerous pathogenetic theories have been proposed but why only a minority of patients with unerupted teeth develop dentigerous cysts remains poorly understood. In one study, 29.6% of maxillary third molars were impacted but the frequency of cyst formation was only 5.4%;[4] and other studies have estimated the ratio of cyst:unerupted tooth to be 1 in 150 and 1.44 in 100, respectively.[5, 6]

The eruption cyst[10] is a superficially located dentigerous cyst, presenting as a bluish swelling of the gum overlying an erupting tooth. They are most commonly seen in children, typically affecting the mandibular first molar and maxillary incisor teeth. Cyclosporin therapy is a recognized predisposing factor.[7, 8]

Depending on the type and position of the associated tooth, many dentigerous and gingival cysts can be treated by marsupialization which generally results in full eruption of the tooth.

LATERAL PERIODONTAL AND BOTRYOID ODONTOGENIC CYSTS

Developmental lateral periodontal cysts are rare (accounting for only 0.7% of jaw cysts). They typically present in older adults and mainly affect mandibular premolars, presenting in a lateral position but not related to pulpal or periodontal inflammation.[9] They are generally asymptomatic and detected incidentally on routine radiological examination. Removal for histological diagnosis is usual. The histological features are distinct: thin, non-keratinized epithelium with focal plaque-like thickenings. The debate on the epithelial source of the lateral periodontal cyst is ongoing. Enucleation is the treatment of choice and recurrence is rare. In contrast, the botyroid odontogenic cyst, the multilocular / multicystic variant, has a propensity to recur and complete surgical removal is the preferred treatment.[10]

GLANDULAR ODONTOGENIC CYST (SIALO-ODONTOGENIC CYST)

Accounting for less than 1% of jaw cysts, the glandular odontogenic cyst is of interest to both clinician and diagnostic pathologist due to its propensity to recur and potentially puzzling histological features. With a peak presentation in elderly males, most cases arise in the anterior mandible, presenting as a slow-growing, painless swelling, and on radiology, a unilocular or multilocular radiolucency. Histologically, the cyst is lined by cuboidal or columnar epithelium with scattered goblet cells and characteristic intra-epithelial gland-like crypts. Important differential diagnoses include botryoid odontogenic cyst, intra-osseous mucoepidermoid carcinoma and metaplasia within a dentigerous cyst. The glandular odontogenic cyst shows more aggressive behaviour than other odontogenic cysts and multilocular lesions have a particular propensity to recur and should be treated by complete excision.[11, 12]

Inflammatory odontogenic cysts

RADICULAR (DENTAL) CYSTS: APICAL, LATERAL, RESIDUAL

These are by far the most common jaw cysts, accounting for 65–70%[13] and ones for which there is a clearly defined etiological agent. They occur in both sexes and over a wide age range. Inflammation at the root apex of a tooth, either as a result of extension of pulpal inflammation and/or necrosis due to deep dental caries, or triggered by loss of tooth vitality following trauma, can lead to proliferation of the epithelial rests of Malassez within the periodontal ligament. Radicular cysts may arise in association with any damaged tooth but there is a tendency for the maxillary incisor teeth to be involved more frequently than other sites.[13]

Many factors are involved in cyst initiation and progression. Cytokines and growth factors released by the inflammatory cells cause epithelial proliferation and also lead to soft-tissue destruction and osteoclast-mediated bone resorption, thus allowing space for an established cyst to grow by expansion. Bacterial endotoxins may also stimulate epithelial proliferation. Within the mass of proliferating epithelium, intercellular oedema and degeneration of the more centrally located cells leads to cavitation. The presence of abundant proteinaceous debris within the resulting lumen leads to increased osmolarity and drawing in of fluid leading to further expansion of the established cyst.

A radicular cyst may present with acute symptoms of pain and swelling but many are asymptomatic and seen as a radiolucency at the root apex on routine dental radiological examination (**Figure 25.7**). The associated tooth is, by definition, non-vital. Some teeth have additional communications between the root pulp canal and the periodontal ligament – one or more lateral canals – and these are the origin of lateral radicular (lateral dental) cysts.

The main differential diagnosis of a radiolucency at, or close to, the apex of an obviously carious or damaged tooth is that of granulation tissue without cyst formation, commonly referred to a periapical granuloma. The size of the radiolucency can be used as a diagnostic guide since radiolucencies greater than 20 mm are highly likely to be cysts and ones below 5 mm are likely to be granulomas.[14]

Theoretically, adequate endodontic treatment with elimination of necrotic, infected and inflammatory debris within the pulp canal should lead to resolution of the cyst but many persist and require surgical removal via apicectomy or tooth extraction. Cysts that persist after removal of the associated tooth are referred to as residual cysts (**Figure 25.8**).

Pathological diagnosis is usually straightforward. Characteristically, the fibrous wall is thick with active acute and chronic inflammation, and the epithelial lining is non-keratinized stratified squamous with areas of hyperplasia and focal ulceration. There are, however, some potential pitfalls. First, it is not unusual to find areas of epithelial metaplasia, with mucous-secreting and ciliated cells leading to a resemblance to respiratory-type epithelium and misdiagnosis as antral mucosa or a sialo-odontogenic cyst; or keratin-forming cells and misdiagnosis as a keratocystic odontogenic tumour. Second, a developmental cyst or even a cystic odontogenic neoplasm may become secondarily inflamed and lose its characteristic appearances and acquire features that can be indistinguishable from a radicular cyst, especially if only a small

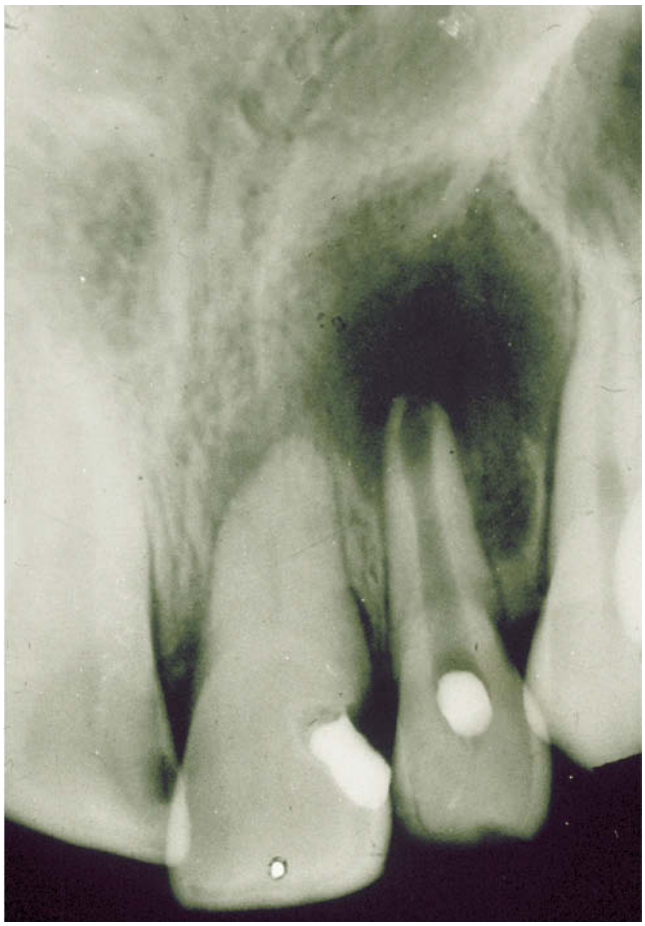

Figure 25.7 Radiological image of radicular cyst upper lateral incisor with typical location.

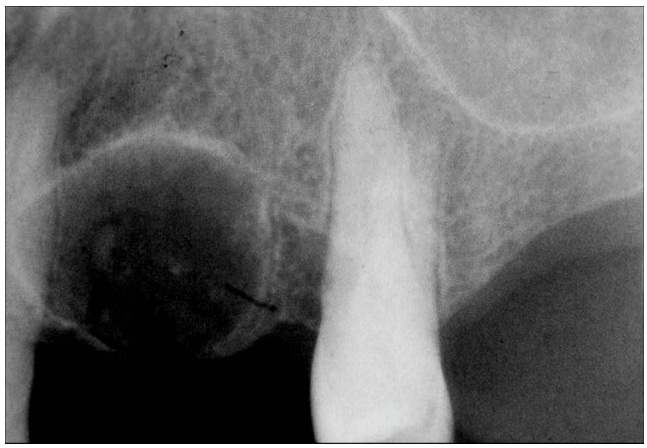

Figure 25.8 Residual cyst; unilocular radiolucency, several years post extraction of a tooth with apical pathology.

portion of the lesion is submitted for histological examination. Submission of any cystic lesion of the jaws should always be accompanied by a brief description of its location in relation to the roots and crown of adjacent teeth; the status of the teeth; and the size, shape, margins and radiodensity of the lesion. A further potential diagnostic pitfall concerns periapical granulomas and radicular cysts following successful endodontic treatment when the inflammation has largely resolved, and there is little, if any, active inflammation. Such lesions should be diagnosed as periapical scar tissue and generally are found as a symptomless radiolucency and probably arise due to a lack of bony infilling following successful endodontic treatment.

PARADENTAL CYST

This inflammatory cyst arises in association with a vital tooth, usually on the lateral aspect, and results from inflammation within a periodontal pocket. The commonest site of occurrence is following pericoronitis around a partially erupted mandibular third molar. Hence, the peak age of presentation is young adults (18–25 years) and males are affected more than females. Paradental cysts account for around 3–5% of jaw cysts. The epithelial origin may be the reduced enamel epithelium or the epithelial cell rests of Malassez in the periodontal ligament.[15] The histological features are similar to the radicular cyst and the correct diagnosis depends on accurate clinical and radiological information. Enucleation is curative.

Non-odontogenic epithelial-lined

NASOPALATINE DUCT (INCISIVE CANAL), MEDIAN PALATINE, MEDIAN ALVEOLAR AND PALATINE PAPILLA CYSTS

The nasopalatine duct cyst and its variants are the most common non-odontogenic cysts accounting for 5–10% of jaw cysts.[16] They arise from epithelial remnants of the vestigial Jacobson's organ (part of the olfactory system in some mammals) within the nasopalatine canal which runs from the nasal septum to the palate in the anterior maxilla immediately behind the maxillary central incisor teeth. The nasopalatine duct cyst presents in the midline of the anterior maxilla. The median palatine and median alveolar cysts are posteriorly and anteriorly located variants, and the palatine papilla cyst is superficially located within the soft tissue of the incisive papilla.

The nasopalatine duct cyst and its variants are seen over a broad age range, peaking in middle-aged adult males. They may present with swelling and pain and may be associated with a salty taste. Many are asymptomatic and identified on routine radiography. The radiolucency is typically symmetrical and heart-shaped with a sclerotic border but may resemble periapical pathology of the incisor teeth. Testing the vitality of the incisor teeth is an important diagnostic step, but in the presence of diseased/non-vital teeth, pathological examination may be necessary for definitive diagnosis. A small nasopalatine duct cyst can be difficult to distinguish from the anterior palatine fossa and asymptomatic lesions less than 10 mm should be observed rather than removed.

The typical histological appearance of the nasopalatine duct cyst is a thick-walled sac, with a lumen lined by both squamous and respiratory type epithelia and often sizeable neurovascular bundles (branches of the long sphenopalatine nerve and vessels) within the collagenous wall. Secondary infection and ulceration may mask the characteristic features making accurate clinical and radiographic information essential. When symptomatic or large, the cysts can be managed by simple enucleation and recurrence is rare.

INTRAOSSEOUS DERMOID AND EPIDERMOID CYSTS

Dermoid and epidermoid cysts[17, 18] generally arise within the soft tissues from entrapped epithelium at lines of embryonic fusion. Rarely, they arise within the bone – in the midline mandible or lateral to the orbit being the most common sites. They generally present in children and young adults, as asymptomatic, well-defined radiolucencies. Histologically, they contain laminated keratin and are lined by orthokeratinized epithelium. Dermal appendages characterize the dermoid cyst and often hairs are found within the lumen. Enucleation is curative.

Non-epithelialized primary bone cysts

SOLITARY (SIMPLE, TRAUMATIC, HAEMORRHAGIC) BONE CYST

Although this is the most frequent of the non-epithelialized bone 'cysts', it occurs mainly in long bones and is uncommon in the jaws. It occurs almost exclusively in the mandible, mainly the molar/premolar regions. Peak incidence is in the second decade.[19] Most are asymptomatic and discovered on routine radiography. Typically, the well-defined radiolucency is scalloped around the roots of the teeth.[20] Around 25% result in bony expansion. Lip paraesthesia is exceptional.[19] Surgical exploration may be necessary for confirmation and reveals an empty intrabony cavity with no obvious soft tissue lining. Curettings consist of delicate loose, vascular fibrous tissue containing scattered osteoclasts and haemosiderin pigment. The favoured pathogenetic theory proposes traumatic intramedullary haemorrhage is followed by failure of organization and subsequent lysis of the blood clot. The interval between trauma and discovery ranges from months to years and the apparent relationship may be spurious. Careful curettage, avoiding damage to tooth roots and neurovascular structures, results in fresh intramedullary haemorrhage, organization of the clot and bony in-filling. Some lesions may resolve spontaneously.

ANEURYSMAL BONE CYST

This rarely affects the jaws with only 60–70 reported cases, mainly in teens/young adults with a slight female predilection.[21] Most arise in the mandibular posterior molar/angle and present as a firm, expansile swelling with

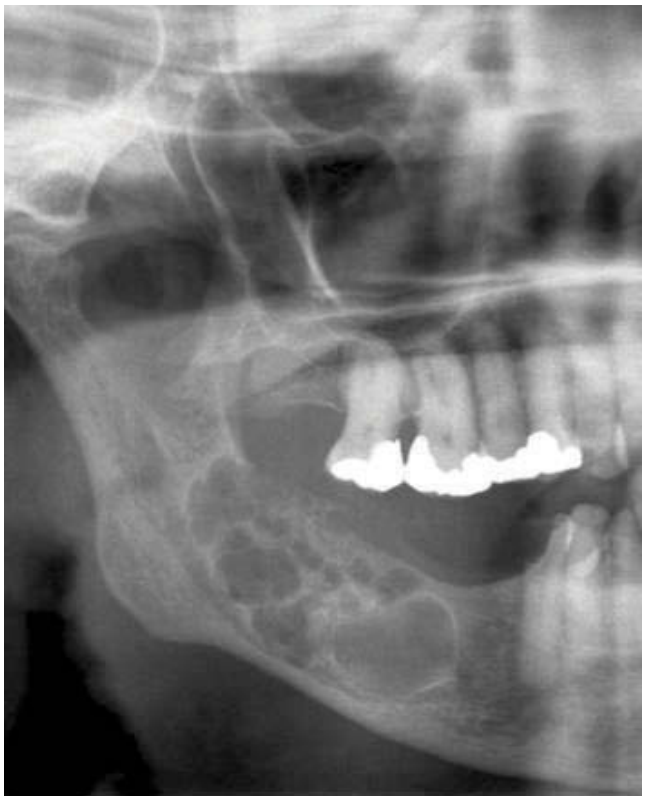

Figure 25.9 Multilocular radiolucency body of mandible: differential includes keratocystic odontogenic tumour, ameloblastoma, odontogenic myxoma, giant cell lesion and haemangioma.

facial deformity and often, pain. Radiographs reveal a uni- or multilocular, balloon or soap-bubble-like radiolucency (similar to ameloblastoma and odontogenic myxoma, **Figure 25.9**). Surgical exploration leads to the characteristic welling-up of blood. The curetted tissue consists of numerous blood-filled spaces without obvious endothelial lining. Multinucleated giant cells and haemosiderin are frequent within the fibrous septae. The pathogenesis is uncertain. In some, a translocation involving chromosome 17 and the oncogene USP6 can be demonstrated suggesting they are neoplastic.[22] Other cases may be associated with an intramedullary haemodynamic disturbance and 20–30% appear to complicate central giant cell granulomas or other fibro-osseous lesions.[23] Curettage is generally curative.

STAFNE'S IDIOPATHIC BONE CAVITY

This uncommon mandibular developmental anomaly may be mistaken as a jaw cyst on radiography[24] when a symptomless round/oval, well-demarcated radiolucency of the premolar-angle region is discovered (**Figure 25.10**). It is located beneath the inferior dental canal and may be bilateral. The appearance is due to a saucer-like concavity of the lingual plate occupied by submandibular salivary gland tissue. Anterior lesions related to the sublingual gland are rare. Sialography is helpful in confirming the diagnosis and can prevent unnecessary surgical exploration.

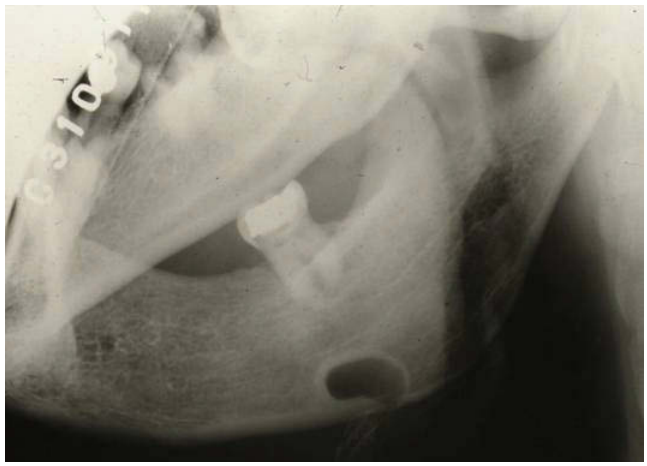

Figure 25.10 Radiology of Stafne's bone cavity; well-defined radiolucency below the level of the ID canal.

FOCAL MARROW-CONTAINING JAW CAVITY (FOCAL OSTEOPOROTIC BONE MARROW DEFECT)

Haemopoietic marrow, typically in the maxillary tuberosity and mandibular ramus/condylar neck, may be mistaken for a cyst radiographically.[25] Histological assessment of curetted tissue is diagnostic.

FIBRO-OSSEOUS LESIONS

These form a diverse group of conditions with differing aetiologies but similar histology (**Figure 25.11**). Normal bone is replaced by variably cellular fibroblastic stroma within which pathological ossification and/or calcification gradually occurs.[26] Diagnosis requires clinical and radiological correlation as well as good knowledge of subtle histological differences. The fibro-osseous spectrum[27–29] includes lesions with a clear developmental aetiology and known genetic mutations, inflammatory/infectious conditions and benign neoplasms. A helpful classification, proposed by Eversole et al,[30] is shown in modified form in **Table 25.4**.

Bone dysplasias

FIBROUS DYSPLASIA

In most cases, fibrous dysplasia (FD) is monostotic and maxillary cases are more frequent than mandibular.[30–33] Maxillary lesions that involve contiguous areas of the zygoma and sphenoid (craniofacial FD) are restricted to a defined anatomical region and generally regarded as variants of monostotic rather than polyostotic FD.[27]

Monostotic FD usually presents in children and young adults or on reactivation of quiescent lesions in adults (for example, during pregnancy) as a painless, slow-growing facial asymmetry or swelling. The smooth, fusiform enlargement is more marked buccally than palatally.[32] Teeth may be displaced or fail to erupt. Involvement of the maxillary sinus and zygomatic process results in exophthalmos and proptosis. Radiographically, the ill-defined

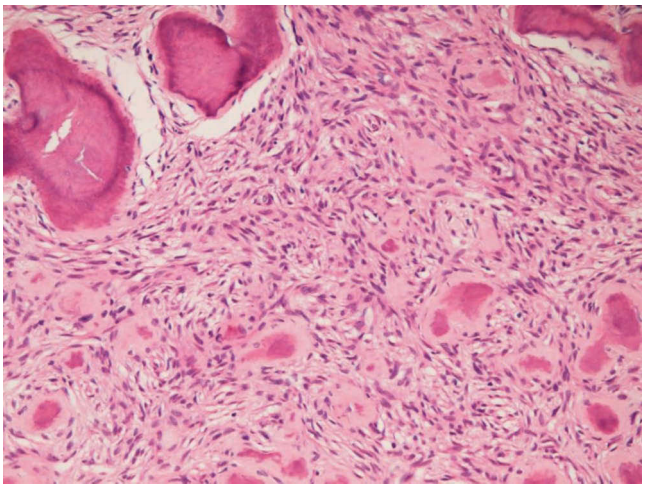

Figure 25.11 Pathological image of a fibro-osseous lesion. This could be an ossifying fibroma or one of the cemento-osseous dysplasias and distinction would require close clinical and radiological correlation.

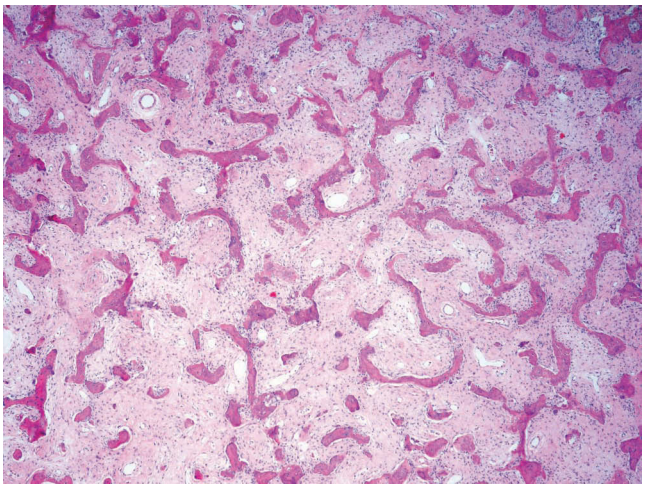

Figure 25.12 Histological picture of typical fibrous dysplasia; cellular fibrous stroma in which so called 'Chinese' character-like trabeculae of bone are deposited.

TABLE 25. 4 A modification of the classification of fibro-osseous lesions of the craniofacial complex proposed by Eversole et al[30]

Pathological process	Disease / condition	Sub-type
Bone dysplasias	Fibrous dysplasia	Monostostic (including craniofacial variant)
		Polyostotic
		Polyostotic with endocrinopathy (McCune–Albright syndrome)
	Osteitis deforms (Paget's disease)	
Cemento-osseous dysplasias	Focal cemento-osseous dysplasia	
	Florid cemento-osseous dysplasia	
Inflammatory / reactive processes	Focal sclerosing osteomyelitis	
	Diffuse sclerosing osteomyelitis	
	Proliferative periostitis	
Metabolic bone disease	Hyperparathyroidism	
Genetic	Cherubism	
Neoplastic	Ossifying fibroma	Ossifying fibroma NOS
		Juvenile ossifiying fibroma (trabecular and psammonatoid types)
		Gigantiform cementoma

lesions merge with normal bone. Early radiolucent lesions pass through mottled and ground-glass/orange-peel stages becoming opaque as bony trabeculae increase in number and size, extending to and distorting, but not crossing, suture lines.

Polyostotic FD mainly affects females (M:F ratio, 1:3), often affecting one side of the body. Most cases present in childhood with bony deformities and pathological fractures, occasionally with skin pigmentation and precocious puberty in females (McCune–Albright syndrome).[32]

Histology depends on the developmental stage of the lesion. Classically, the delicate trabeculae of newly-formed, woven bone resemble Chinese characters and are gradually remodelled to lamellar bone as the lesion ages (**Figure 25.12**).[32] The margin merges with surrounding normal bone, an important distinction from ossifying fibroma (see later).

FD is a sporadic (non-inherited) developmental disorder caused by mutation of somatic cells in fetal (polyostotic FD) or postnatal (monostotic FD) life resulting in alterations in osteoblast growth/differentiation due to faulty expression/signalling of the *GNAS1* gene which encodes for a stimulatory protein.[32] Lesions tend to become quiescent and management is mainly aesthetic reduction of deformity. Lesions are not radiosensitive. Radiotherapy is contraindicated and may increase the risk of transformation to fibro-/osteosarcoma.

OSTEITIS DEFORMANS (PAGET'S DISEASE OF BONE)

This occurs mainly in older adults and many cases are subclinical.[30, 34] Skull involvement is common and often associated with jaw lesions (mainly maxillary). Presentation includes bone pain and deformity, spacing

of teeth, difficulty with dentures, and motor/sensory deficit due to cranial nerve compression. In early lesions, increased bone vascularity results in post-extraction haemorrhage. Hypercementosis and ankylosis, common in later stages, make for traumatic extractions, thus exacerbating poor healing due to late-stage ischaemia. Radiographically, lesions are ill-defined, initially osteoporotic, gradually becoming osteosclerotic ('cotton-wool patches'). Histologically,[34] osteoclastic activity dominates early lesions. Resorbed bone is replaced by vascular, cellular fibrous tissue. Gradually, trabeculae of new bone are deposited and remodelled with prominent resting and reversal lines (mosaic bone). Serum alkaline phosphatase is raised in active disease and useful in monitoring treatment.[34]

Osteitis deformans results from osteoclast dysfunction.[34] Aetiology is unclear, possibly involving paramyxovirus infection and genetic predisposition (on chromosome 18q). Treatment is with calcitonin and/or bisphosphonates. Osteosarcoma is a rare complication mainly affecting cases with widespread lesions.

Cemento-osseous dysplasias

These non-neoplastic proliferations are subdivided into focal and florid based on differences in location and number of lesions (**Figure 25.13**).[34–37] COD is more prevalent in females than males (M:F ratio, 1:10), and in Blacks with most cases presenting after 30 years. Focal COD[36] is more common, and seen as multiple periapical lesions of mandibular incisors which are asymptomatic being discovered on routine radiographs. Early lesions are rounded radiolucencies, which become increasingly radiopaque (maintaining a narrow radiolucent rim) as bone/calcified acellular cementum-like tissue is deposited.[38] Related teeth are vital (in contrast to periapical granulomas/radicular cysts). Florid COF[36] affects all four quadrants and may cause jaw expansion or symptoms related to ulceration/infection. Gigantiform cementoma[37, 38] is a rare familial variant sometimes categorized as neoplastic. Histologically, in CODs, new bone and rounded cementum-like globules are increasing deposited within the fibrocellular stroma eventually leading to a solid, bone-like mass. COD is self-limiting and treatment (for cosmesis or infection) is rarely needed.

Inflammatory/reactive processes

SCLEROSING OSTEOMYELITIS (SO)

This is a form of non-suppurative chronic osteomyelitis[33, 34] and is usually a localized reaction to low-grade periapical inflammation or infection although bacteria are not readily cultivable. Focal lesions affect mainly the mandibular premolar/molar region in children and young adults and present as a localized, uniform radiodensity

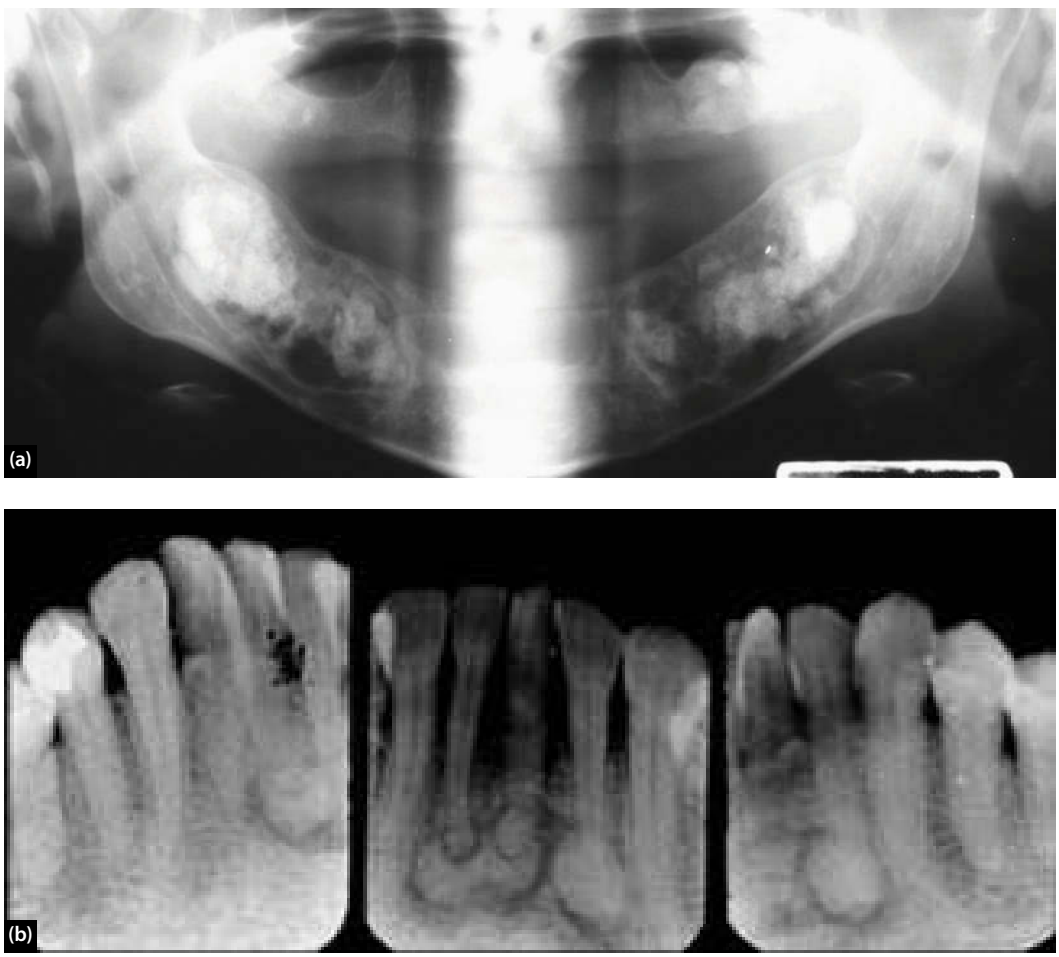

Figure 25.13
(a) Radiological appearances of florid cemento-osseous dysplasia and **(b)** periapical cemento-osseous dysplasia **(b)**.

related to the tooth root apex without jaw expansion. Histologically, dense sclerotic bone with scant fibrous connective tissue or inflammatory cells is seen. The diffuse form of SO affects adults[33, 34] and resembles florid COD radiographically. Treatment of SO is elimination of the source of inflammation by extraction or endodontic therapy. Sclerotic areas may remain radiographically.

PROLIFERATIVE PERIOSTITIS (GARRE'S OSTEOMYELITIS)

Mainly affecting adolescents, this form of chronic osteomyelitis results in onion-skin thickening and swelling of the mandibular lower border due to periosteal reaction to periapical inflammation.[30, 34] Histologically, highly cellular, woven bone is arranged in parallel layers. The bone gradually remodels 6–12 months following elimination of infection.

Metabolic bone disease: Hyperparathyroidism

The jaws may be affected as part of the multifocal replacement of bone by brown tumours, collections of osteoclasts within a vascular, haemosiderin-rich stroma.[30, 33, 34] Primary hyperparathyroidism (HP) due to parathyroid hyperplasia or adenoma mainly affects post-menopausal females. Radiolucent cyst-like lesions may be seen together with loss of lamina dura around tooth roots. Blood biochemistry is essential in interpreting the histological features which are indistinguishable from a giant-cell granuloma. Bone lesions due to the secondary HP associated with chronic renal failure are more common. The bone lesions of HP reverse on treatment of primary HP and respond to oral vitamin D in secondary HP.

Genetic: Cherubism

This is inherited as an autosomal trait (mapping to chromosome 4p16.3), but due to weaker penetrance in females, the phenotype is more common in males.[30, 33, 34] Onset usually occurs before the age of 7 years, presenting with swelling of the mandibular angles and in severe cases, the posterior maxillae, resulting in chubby face, interference with speech and swallowing, displacement/loosening of teeth and cervical lymphadenopathy (due to reactive hyperplasia). Maxillary involvement results in the eyes appearing to turn upwards. Radiography reveals multilocular radiolucencies with fine bony septae. Histologically, early lesions resemble giant cell granulomas with focal collections of multinucleated giant cells within cellular and vascular fibrous tissue. Vessels may show a hyaline cuff. Older lesions show increasing bony repair. Initial rapid growth slows on puberty and lesions gradually regress. Treatment by curettage or paring down is rarely needed.

Neoplastic: Ossifying fibroma and cemento-ossifying fibroma

Although neoplastic, traditionally ossifying fibroma (OF) and cemento-ossifying fibroma (COF)[30, 33] have been categorized with the fibro-osseous jaw lesions, and are considered part of a spectrum rather than two separate lesions. They present slowly as an expansile, well-circumscribed, painless swelling mainly affecting the mandibular premolar or molar regions. Females are more commonly affected than males with a peak incidence between 20 and 40 years of age. Radiographically, lesions are well-defined, initially radiolucent but with increasing calcifications centrally and eventually becoming mainly radiopaque with a narrow radiolucent rim. Roots of related teeth may be displaced. Histological appearances match the radiographic appearances being initially fibrous and cellular, later developing trabeculae of woven bone with peripheral osteoblasts, dystrophic calcifications and rounded cementicles.[38] The calcifications fuse with maturation eventually forming a dense calcified mass with a peripheral fibrous zone which allows the lesion to shell out from the adjacent bone during surgical enucleation.

Juvenile active (aggressive) OF affects the maxilla in children and adolescents[39] and histologically[40] the stroma is often highly cellular and the calcification pattern either trabecular (mainly osteoid with plump osteoblasts) or psammomatoid (compact, rounded calcifications). Some lesions are locally aggressive with a tendency to recur, but most respond to conservative surgery.

TUMOURS (NEOPLASMS)

Tumours arising from bone cells

OSTEOMAS

Osteoma, a benign neoplasm of bone, is subclassified into 'compact' (cortical) and 'cancellous'.[34] They can be situated on the surface of the bone and present as hard swellings (exostosis) or alternatively, can exist purely within the substance of the bone (enostosis, dense bone island) and in the latter location would likely be an incidental radiological finding. Some probably represent developmental anomalies or reactive hyperplasias rather than true neoplasms, common examples being mandibular tori (bilateral exostoses on the lingual aspect of the mandible in the premolar region) and palatine torus (a mushroom-like swelling in the midline of the palate). The most common site for a true osteoma is in the paranasal sinuses. Generally, tori present in childhood and grow slowly, and can be removed for cosmetic reasons or before fitting a denture. Multiple osteomas may be the presenting features of Gardner syndrome (**Figure 25.14**),[41] often leading to the diagnosis (and management by prophylactic colectomy) before adenocarcinomatous transformation of the familial colonic polyps.

OSTEOID OSTEOMA, OSTEOBLASTOMA

These are benign neoplasms of bone with 80% involving long bones and only 1% involving the jaws.[34] Most present in young adult males with severe pain which is relieved by aspirin. Osteoid osteomas are typically <2 cm in size while osteoblastomas are larger and more likely to present with swelling.[34] Radiography reveals a radiolucency

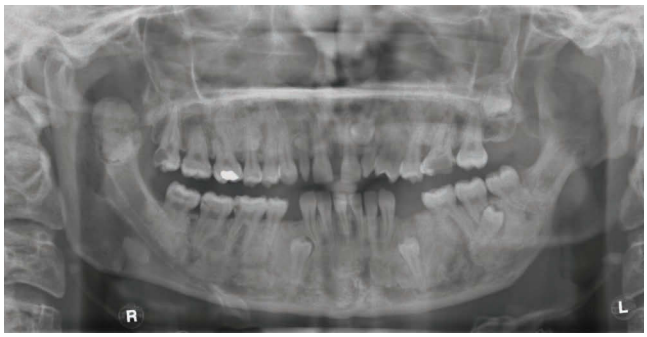

Figure 25.14 Gardner syndrome patient: multiple osteomas seen as radiodensities along with unerupted and supernumerary teeth.

with sclerotic rim and intralesional speckled calcification. Surgical exploration reveals a gritty lesion with well-defined boundaries, which shells out easily.

Histologically, a loose fibrovascular stroma containing abundant trabeculae of osteoid rimmed by plump osteoblasts and mineralized trabeculae is evident. Diagnosis of bony lesions should only be made when clinical and radiographic details are known since the plump osteoblasts could lead to an erroneous diagnosis of osteosarcoma especially when only curettings are available.

OSTEOCHONDROMA

This cartilage-capped exostosis is rare in the jaws, occurring mainly in the mandiblular condyle and coronoid process.[34] Differentiation from condylar hyperplasia can be difficult. Peak presentation is in females in the 4th–5th decade.[42] The slow-growing swellings cause progressive deformity. Histologically, both the overgrowth of bone and its cartilage cap are entirely benign. Any cellular atypia, especially within the cartilage, may indicate development of a secondary chondrosarcoma, a rare but well-documented occurrence.[33]

OSTEOSARCOMA

This is a malignant bone-producing tumour,[34] with only 6–10% of cases involving the jaws.[43–47] The average age at presentation of jaw lesions is 30–40 years, a decade more than for lesions at other sites. Most develop sporadically with no obvious aetiological factors. 'Secondary' osteosarcomas arise following radiotherapy or in Paget's disease of bone, FD, and in association with hereditary retinoblastoma, Ollier disease and Li-Fraumeni syndrome.

Swelling, pain, paraesthesia, ulceration and loose teeth are common presenting features.[46, 47] The radiographic appearance depends on the proportion of radiolucent soft tissue to radiopaque malignant bone matrix. The classical 'sunray' appearance results from the perpendicular spicules of periosteal new bone. Widening of periodontal ligament spaces and the inferior alveolar canal are other classical changes. Histological diagnosis requires the demonstration of osteoid and bone by overtly malignant cells. The architecture of the malignant bone is abnormal ('lace-like'). A high proportion of jaw lesions also contain malignant cartilage (chondroblastic osteosarcoma) while bone is scanty in some (fibroblastic osteosarcoma).

Osteosarcomas arising on the bone surface present specific characteristics and behaviours.[34, 46, 47] The parosteal osteosarcoma is a low-grade neoplasm which can mimic osteochondroma if a cartilage cap is present and also end-stage FD, highlighting the need for close radiological correlation and submission of reasonable quantities of lesional tissue for pathological diagnosis. The malignant cells are generally bland but some focal atypia should be demonstrable. Periosteal osteosarcomas are exceptionally rare and although generally clinically indolent, display more overt malignant cytological features and often abundant cartilage admixed with the malignant bone.

Surgery is the mainstay of treatment with the aim of achieving clear margins.[59] The 10-year survival is 59% in one series[45] with local recurrences more frequent than distant metastasis (31% versus 21%). Pre-surgical or adjuvant chemo- and radiotherapy may offer some benefits. The rarity of jaw osteosarcoma makes it difficult to assess the effectiveness of the well-defined protocols that exist for long-bone osteosarcoma. Overall, it is considered that the prognosis of osteosarcoma of jaws is better than long bones with 40% 5-year survival for jaw lesions compared with 20% at other sites.[43, 44]

CHONDROMA, CHONDROSARCOMA

These are rare in the jaws; the most common sites being the anterior maxilla and mandibular condyle, presenting mainly in middle age with pain, swelling and loosening of teeth.[34, 48, 49] Histologically, the chondroma is a cytologically benign tumour forming mature cartilage. A high degree of cellularity, multiple chondrocytes occupying a single lacuna and plump/binucleate cells are suspicious of well-differentiated chondrosarcoma.[34, 48] Demonstration of invasion is also important. Less well-differentiated chondrosarcomas exhibit more obvious cytological features of malignancy. Calcification and endochondral ossification may occur in both benign and malignant lesions and accounts for the variable radiographic appearances. The outline may be well- or ill-defined or multilocular. Signal characteristics typical of cartilage matrix can best be seen on CT scanning. As in osteosarcoma, the rarity means evidence-based treatment protocols are not yet established. Surgery is the mainstay of treatment with 60% 5-year survival.[49] Mandibular compared to maxillary lesions, small tumour size and high degree of differentiation are favourable prognostic features, the first two presumably reflecting the importance of achieving surgical clearance.

Odontogenic tumours

Odontogenic tumours, a spectrum of lesions unique to the jaws, are derived from tooth-forming apparatus.[50] They range from hamartoma-like dental malformations (odontomas) through to benign neoplasms, locally invasive growths, malignant neoplasms with metastatic potential

TABLE 25.5 Classification of odontogenic tumours (a modification of WHO classification[50])

Benign odontogenic tumours	
Arising from odontogenic epithelium only	Ameloblastoma
	Squamous odontogenic tumour
	Calcifying epithelial odontogenic tumour
	Keratocystic odontogenic tumour (formerly, odontogenic keratocyst)
Including odontogenic epithelium as well as ectomesenchyme with or without hard tissue formation	Ameloblastic fibroma
	Ameloblastic fibro-dentinoma and fibro-odontoma
	Complex and compound odontoma
	Calcifying cystic odontogenic tumour
	Dentinogenic ghost cell tumour
Arising from odontogenic ectomesenchyme only	Odontogenic fibroma
	Odontogenic myxoma
	Cementoblastoma
Malignant odontogenic tumours	
Odontogenic carcinomas	Metastasizing (malignant) ameloblastoma
	Ameloblastic carcinoma • Primary type • Secondary type (dedifferentiated)
	Primary intraosseous carcinoma • Solid type • Arising from keratocystic odontogenic tumour • Arising from other odontogenic cysts
	Clear cell odontogenic carcinoma
	Ghost cell odontogenic carcinoma
Odontogenic sarcomas	Ameloblastic fibrosarcoma
	Ameloblastic fibro-dentino-sarcoma and fibro-odontosarcoma

to primary intraosseous carcinomas with few, if any, odontogenic features. An abbreviated form of the WHO classification,[50] based on behaviour and pathogenesis, is shown in **Table 25.5**. Odontomas account for around one-third. Of the true neoplasms, excluding the keratocystic odontogenic tumour, recently redesignated as an odontogenic tumour, the ameloblastoma is as common as all other types combined. Diagnosis depends on clinical and radiological features as well as the precise histology, hence, accurate information on location, relationship to teeth, circumscription and radiodensity should be submitted to the reporting pathologist.[51] Odontogenic tumours tend to reflect morphological features and inductive interactions of normal tooth germs and histological distinction between some tumours relies on subtle features. The rarity of many lesions, and hybrid forms, add to the diagnostic challenge.

BENIGN ODONTOGENIC TUMOURS

Ameloblastoma

Although the most common odontogenic neoplasm,[52] ameloblastoma only accounts for around 1% of oral biopsies.[53] Based on clinical, radiographic, histological, behavioural and prognostic features, four subtypes[52] can be distinguished (**Table 25.6**). In addition, two malignant forms and a benign variant in which dental hard tissues develop are recognized (**Table 25.6** and see later).

Solid / Multicystic (Conventional) Ameloblastoma

Solid/multicystic (conventional) ameloblastoma (SMA), the most common type of ameloblastoma, displays benign but locally invasive growth with a high recurrence rate if not removed adequately.[52, 54] It is derived from rests of the dental lamina but trigger factors are unknown. The most common site is mandibular molar-ramus and the mandibular: maxillary ratio is around 5:1. All age groups are affected (mean, 37 years) with a M:F ratio of 1.2:1. SMA is centrally located within the jaw and hence, there are few clinical signs in early stages. Later, there may be increasing facial deformity, loosening of teeth, eggshell crackling, bone perforation and spontaneous jaw fracture. Radiographically, multilocular destruction of bone creates a soap-bubble (honeycomb) appearance (**Figure 25.9**). The scalloped margin may incorporate tooth roots typically showing resorption. Some SMA occurs in a dentigerous relationship with an unerupted tooth. At operation, the tumour appears as a greyish-white mass replacing bone. The cut surface is variously solid and cystic. Histologically,[52] the lesion consists of odontogenic epithelium within a fibrous stroma. The odontogenic epithelium shows two

TABLE 25.6 Classification of ameloblastomas and related odontogenic tumours

Benign odontogenic neoplasm	Subtype	Histological variants / key features
Ameloblastoma	Classic solid/multicystic (SMA)	Follicular
		Plexiform
	Unicystic (UA)	Luminal type
		Intraluminal type
		Intramural type
	Peripheral (extra-osseous) ameloblastoma (PA)	
	Desmoplastic ameloblastoma (DA)	
Odontoameloblastoma		Growth features are similar to SMA but contains dysplastic dentine and enamel
Malignant odontogenic neoplasms		
Metastasizing ameloblastoma		A retrospective diagnosis: typical histology but distant metastases occur
Ameloblastic carcinoma		Cellular atypia present

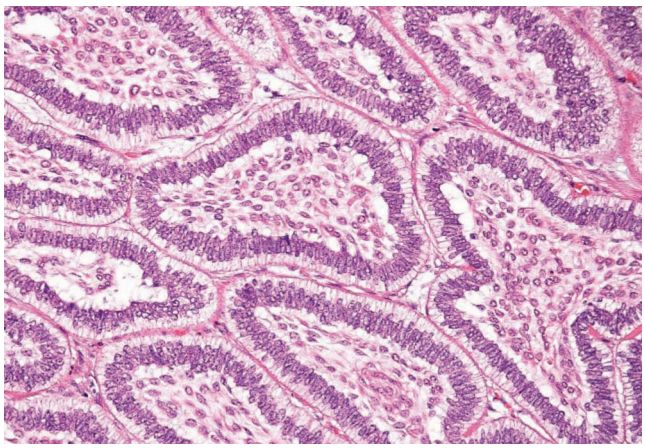

Figure 25.15 Histological image of follicular ameloblastoma. Tumour islands exhibit typical peripheral palisading, reverse polarity and there are central more loosely cohesive stellate reticulum like cells.

main patterns, follicular and plexiform, but many lesions comprise both. Each follicle/strand consists of outer, columnar ameloblast-like cells and inner stellate reticulum-like cells (**Figure 25.15**). Cysts may develop within the stellate cells (especially in the follicular pattern) or within the stroma (especially in the plexiform pattern). The stellate reticulum-like cells are more obvious in the follicular pattern and may display features of the spindle cell, basal cell, granular cell, acanthomatous (squamous), ghost cell or other, less common, histological variants.[52] The tumour infiltrates within the cancellous bone leading to poorly defined margins. The preferred treatment is *en bloc* resection since cancellous infiltration may extend 5mm or more beyond the radiological limits. A conservative approach (enucleation, curettage and burring the bone cavity followed by close review of healing) may be considered for small mandibular lesions. All maxillary lesions should be treated radically since the consequences of recurrence involving the skull base are severe with a mortality of up to 60%.[52, 54]

Unicystic Ameloblastoma

Unicystic ameloblastomas (UAs)[52] account for 5–15% of all ameloblastomas.[55] The term should be reserved for well-defined, monocystic lesions with a lining focally composed of ameloblastomatous epithelium (type I, luminal UA). The inner surface of the cyst lumen may show one or more polypoid, pedunculated masses (type II, intraluminal UA) or intramural nodular growths (type III, intramural UA). Types I and II tend to be in a dentigerous relationship although on removal, the involved tooth is displaced by the cyst rather than projecting into the lumen. Pathogenesis is controversial, theories including an origin from a pre-existing odontogenic cyst, ameloblastic transformation of reduced enamel epithelium, and cystic degeneration and subsequent fusion of microcysts within a SMA. The posterior mandible is the most common site (maxilla: mandible ratio, 1:5). Teens and young adults are mainly affected without an obvious gender distribution. Usual presentation is a painless swelling. Radiographically, UA may be unilocular or multilocular. Root resorption is common. Diagnosis requires assessment of the complete cyst and categorization based on findings in both the epithelial cyst lining and fibrous cyst wall. Types I and II are usually treated conservatively by enucleation and curettage. Type III shows a greater tendency to recur and is generally managed as SMA.

Peripheral (extra-osseous) ameloblastoma (PA)

These comprise 2–10% of all ameloblastomas and are thought to arise from extra-osseous residues of dental lamina (glands of Serres) or the basal layer of the oral mucosa.[52, 56] Around 70% affect the mandible, mainly premolar region. All ages are affected (mean, 52 years) with a M:F ratio of 1.9:1. PA presents as a painless, sessile, firm, 1 cm gingival/alveolar growth. The surface may be smooth, granular or warty. Colour varies from normal to deep red. Masticatory trauma may result in ulceration or frictional keratosis. In most cases, there is

no radiological evidence of bone involvement but large lesions may cause superficial saucerisation. Many PA are removed as suspected fibrous or inflammatory epulides. Histological features resemble SMA. PA are rare and the histological differential diagnosis includes peripheral odontogenic fibroma, squamous odontogenic tumour and odontogenic gingival epithelial hamartoma. PA does not invade bone and recurrence is rare after conservative supraperiosteal surgical excision with adequate (disease-free) margins.

Desmoplastic Ameloblastoma (DA)

This variant[52, 57] of SMA (accounting for 4–13%) exhibits locally infiltrative growth. In contrast to the other ameloblastoma categories, maxillary lesions are as common as mandibular. Lesions present over a wide age range. Males and females are equally affected. Initial usual clinical complaint is a painless swelling, 1–8 cm in size. Radiographically, the borders are ill defined (in contrast to other ameloblastomas) and around 50% are mixed radiolucent/radiopaque potentially leading to a pre-operative diagnosis of fibro-osseous lesion. Resorption of tooth roots is common. The tumour appears as a solid, white infiltrative growth. Histologically,[58] the irregularly shaped islands and cords of odontogenic epithelium are embedded in a densely fibrous stroma often with osseous metaplasia. Focal peripheral pallisading is seen but central areas are hypercellular, whorled spindle or acanthomatous cells rather than stellate reticulum-like. Radical resection is favoured and recurrence rates resemble those for SMA.

Squamous odontogenic tumour (SOT)

This rare benign, locally infiltrative tumour[59, 60] develops from the rests of Malassez within periodontal ligament of vital, erupted teeth and mainly affects the mandible. A wide age range, slight male predominance, and occasional multicentric lesions are reported. Tooth mobility, local pain, gingival swelling/erythema and bony expansion are typical presenting features. Radiographically, a unilocular (or in larger lesions, multilocular) rounded or triangular radiolucency between the roots of adjacent teeth is usual. Histologically, rounded islands of well-differentiated squamoid epithelial cells are embedded in a fibrous stroma. The differential diagnosis includes ameloblastoma, intra-osseous squamous cell carcinoma and 'squamous odontogenic tumour-like islands arising within the walls of odontogenic cysts'. Recurrence is rare after complete, conservative surgical treatment.

Calcifying epithelial odontogenic tumour (CEOT, Pindborg tumour)

CEOT,[61, 62] a locally invasive epithelial neoplasm, accounts for around 3% of odontogenic tumours. The mandibular: maxillary ratio is 2:1. Peak age of presentation is 40 years with most cases presenting between 20 and 60 years. There is no gender predilection. Usual presentation is asymptomatic, slow-growing expansile jaw mass. Radiographically, the unilocular/multilocular, mixed radiolucency-radiopacity may be associated with an unerupted tooth, most often a mandibular third molar. The tumour is solid and histologically consists of islands and sheets of polyhedral cells with conspicuous intercellular bridges embedded within a fibrous stroma. Important diagnostic features include the marked nuclear pleomorphism including giant/monster forms but lack of mitotic figures (unless the tumour has undergone malignant change); and the eosinophilic hyaline material within or around the tumour cells which is positive with stains for amyloid and frequently shows concentric rings of calcification. Differential diagnosis includes intraosseous squamous cell carcinoma, metastatic carcinoma, and, if clear cells are evident, a salivary gland neoplasm. Attention to cellular details such as the lack of mitotic figures and the amyloid globules should prevent a misdiagnosis. CEOT is locally invasive and local resection is needed except for small lesions where enucleation may be sufficient. The overall recurrence rate is around 15% but is higher after enucleation, in larger tumours and in the clear cell variant.

Adenomatoid odontogenic tumour (AOT)

This slowly progressive odontogenic epithelial lesion[63, 64] accounts for around 3% of odontogenic tumours and may be harmatomatous rather than neoplastic. It predominantly affects the maxilla (maxilla:mandible ratio, 2.1:1), females (M:F ratio, 1:1.9), and younger ages (90% < 30yrs). Most cases arise in association with the follicle of an unerupted canine presenting as a painless palpable bony-hard swelling and radiographically as a well-defined unilocular 'dentigerous' radiolucency often with discrete radiopaque foci. Intraosseous periapical and interdental, and peripheral (gingival) variants are less common. Histologically, the tumour is well circumscribed and encapsulated, consisting of variably sized nodules of cuboidal and columnar odontogenic epithelium, some with a characteristic glandular formation, embedded within a sparse fibrous stroma with droplets of eosinophilic amorphous material. Enucleation or curettage is curative. Recurrence is rare.

Keratocystic odontogenic tumour (KCOT), formerly odontogenic keratocyst

Formerly called 'odontogenic keratocyst', the KCOT[65] was renamed at the WHO Consensus Conference, 2003,[50] to reflect its neoplastic nature.[66–68] It is now designated a benign, uni-/multicystic odontogenic tumour with potential aggressive, infiltrative behaviour.[69] It is one of the most common odontogenic tumours, peaking in the 2nd and 3rd decades, with a M:F ratio of 1.6:1. Around 75% occur in the mandible, mainly in the molar-angle-ramus region. Many cases are asymptomatic presenting radiographically as a radiolucency, either small and round-ovoid, or larger with scalloped border (**Figure 25.16**). Large lesions may present with pain, swelling, discharge, pathological fracture and if cortical bone is penetrated, soft tissue involvement.

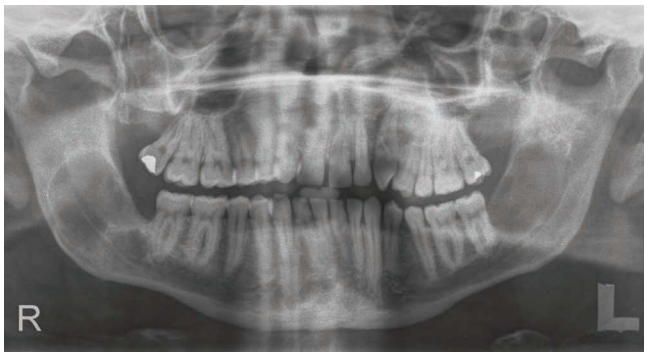

Figure 25.16 OPG of patient with Gorlin Golltz syndrome demonstrating three distinct radiolucencies: LLQ, LRQ and ULQ.

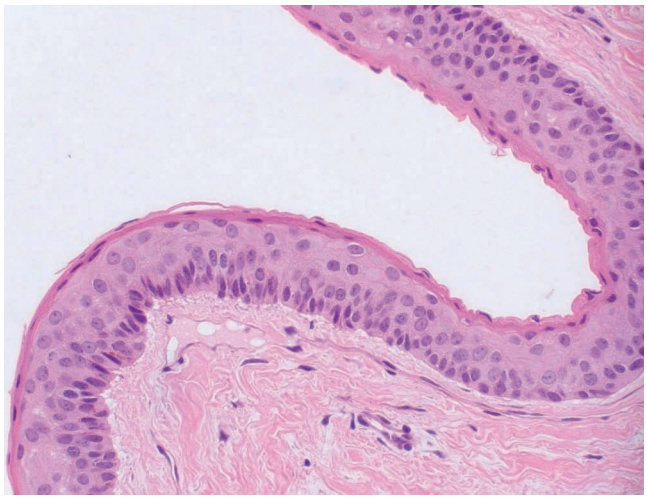

Figure 25.17 Parakeratinized epithelium characteristic of keratocystic odontogenic tumour.

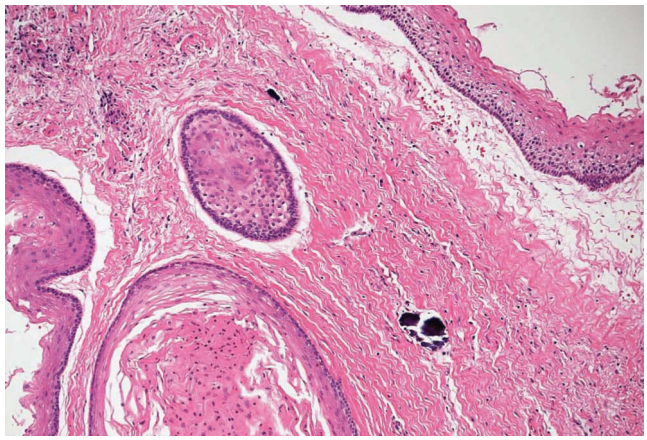

Figure 25.18 Daughter or satellite cysts in keratocystic odontogenic tumour from syndromic patient.

TABLE 25.7 The most common features of naevoid basal cell carcinoma syndrome

Features of naevoid basal cell carcinoma syndrome
Multiple keratocystic odontogenic tumours – either simultaneous or sequential
Basal cell carcinomata - multiple, often in non-sun-exposed skin sites
Frontal and temporoparietal bossing, hypertelorism, mandibular prognathism
Calcification of the falx cerebri
Bifid or deformed ribs
Medulloblastoma, abdominal neoplasms

Adjacent teeth may be displaced but root resorption is rare. The cyst lumen is full of creamy material – keratin squames – and the cyst wall is thin and lined by a thin, parakeratinized epithelium (**Figure 25.17**).

Odontogenic epithelial residues are frequent in the cyst wall and may give rise to satellite cysts (**Figure 25.18**). Budding of the cyst lining is less common but can give rise to daughter cysts. Mitotic figures may be present within suprabasal layers of the epithelial lining and other dysplastic features are occasionally seen and may herald malignant transformation.

Multiple KCOT (either simultaneous or sequential) are an important part of the inherited naevoid basal cell carcinoma syndrome (NBCCS, Gorlin Syndrome, Gorlin and Goltz Syndrome).[1, 70] **Table 25.7** shows the more common clinical features of the syndrome, and notable differences between non-syndrome sporadic and syndrome KCOT are shown in **Table 25.8**.

TABLE 25.8 A summary of clinical and histological features of keratocystic odontogenic tumours in non-syndrome and naevoid basal cell carcinoma syndrome patients

Non-syndrome KCOT	NBCCS KCOT
Single	Multiple – either simultaneous or sequential
Maxilla:mandible ratio, 1:3	Maxilla:mandible ratio, 1:1
Peak age, 20–40 years	Peak age, 15–30 years
Radiographically, generally small round-ovoid and unilocular	Radiographically, frequently large and multilocular
Few proliferating odontogenic epithelial residues and satellite cysts	Proliferating epithelial residues (some 'ameloblastomatous') and frequent satellite cysts
Rarely budding of main cyst lining or presence of daughter cysts	Occasional budding of main cyst lining and presence of daughter cysts
Recurrence rare after complete removal	Recurrence and further new cysts expected

The source of odontogenic epithelium giving rise to the KCOT is uncertain. The dental lamina and its remnants are favoured but there is some evidence for extensions of basal cells from overlying oral epithelium – the original source of the dental lamina in the embryo/infant.[1, 76] The genetic basis of KCOT[1] lies in the NBBCCS or PCTH gene, a tumour suppressor gene on chromosome 9q22.3-q31 which may suffer allelic loss leading to over-expression of bcl-1 and TP53. Over-expression and amplification of genes located in 12p may also be involved.

KCOT has a tendency to recur and the rate depends on the original treatment (overall recurrence rate, 20–25%). Local resection and enucleation with peripheral ostectomy and Carnoy's solution are curative while enucleation with peripheral ostectomy, enucleation alone, marsupialization and enucleation with Carnoy's solution are associated with increasing risk of recurrence (18%, 26%, 40% and 50% respectively in a recent systematic review).[71]

Ameloblastic fibroma, ameloblastic fibro-dentinoma, ameloblastic fibro-odontoma (AF, AFD, AFO)

AF is a rare, benign neoplasm of both odontogenic epithelium and ectomesenchyme.[72, 73] The presence of dentine or other dental tissues leads to the designation ameloblastic fibro-dentinoma[73] (AFD) and ameloblastic fibro-odontoma (AFO),[73, 74] respectively.

Most AF are found in the posterior mandible, presenting as painless swelling or on investigation of disturbed tooth eruption. The peak age is 15 years and there is no sex predilection. Radiographically, a well-demarcated, uni- or multilocular radiolucency with a sclerotic rim is typical. Histologically, strands and islands of odontogenic epithelium forming knots with peripheral palisading (each knot resembles a normal developing tooth germ) are embedded in a cell-rich ectomesenchyme resembling dental papilla. Differential diagnosis includes ameloblastoma (in which the stroma is mature and fibrous rather than immature, cell rich and myxoid); enlarged/hyperplastic dental follicle (scanty epithelium; typical location overlying unerupted tooth); and when hard tissues are evident, the AFD and AFO. Enucleation and curettage is generally curative. Recurrence may follow incomplete removal and rarely, progression to malignancy (ameloblastic fibrosarcoma) is reported.[72]

Odontomes

Odontomes[75–77] are dental hamartomas rather than neoplasms, and range from malformed teeth at one end of the spectrum through to masses of haphazardly arranged enamel, dentine and cementum (composite odontomes). A malformed tooth may replace one of the normal series in either the deciduous or permanent dentition and well-recognized forms include the dens-in-dente (dilated gestant), geminated, and taurodont. The diagnosis of a mature malformed tooth is obvious on radiography but immature forms are radiolucent with variable focal radiopacities (increasing as maturity is reached). Treatment depends on symptoms, location and dental factors and most cases require surgical removal.

The **compound odontome**[75, 76, 78] consists of a varying number of miniature teeth (denticles/odontoids) within a fibrous sac. The anterior maxilla is the usual site but they are found in any tooth-bearing area of both jaws. They are diagnosed mainly in children and adolescents, show no sex predilection, and are one of the most common odontogenic hamartomas/tumours. Once fully mature, growth ceases (generally at 1–2 cm in diameter) and jaw swelling is unusual. Most cases are diagnosed when they impede eruption of a nearby tooth or cause displacement of an erupted tooth. Multiple compound odontomes may be sporadic or part of Gardner syndrome.[34, 79] Radiologically, the denticles and surrounding fibrous sac (radiolucent peripheral zone) are usually obvious. Macroscopic assessment of the specimen may be sufficient to make a definitive diagnosis. Demineralized sections show the denticles, and depending on maturity, immature enamel, dentinoid, cementoid and variable amounts of odontogenic epithelium, dental papilla and reduced enamel epithelium. Enucleation is curative and recurrence does not occur.

The **complex odontome**[80] is also common in children and adolescents of both sexes. The most frequently affected tooth bearing site is posterior mandible. They tend to grow to 3–6 cm in diameter and generally present as slowly increasing, painless swelling, often associated with impairment of eruption or displacement of adjacent teeth. The typical radiographic appearance of a maturing lesion is a spherical/ovoid radiopacity with a radiating periphery and surrounding radiolucent zone. Local enucleation is generally curative but recurrence may follow incomplete removal of an immature lesion. Histological assessment of mature complex odontomes shows variable amounts of enamel, dentine and cement, haphazardly arranged and surrounded and supported by a collagenous capsule containing strands and islands of odontogenic epithelium. Developing lesions show more unmineralized dental tissues and cellular areas of soft tissue. The distinction from the compound odontome is not clear cut.[81] Immature forms may contain AF-like areas leading to uncertainty about the true nature of the AF and its variants which some workers consider represent immature odontomes.[72, 73]

Odontoameloblastoma

This extremely rare tumour[82] is similar to an SMA but contains hard dental tissues. Most lesions present in the posterior mandible, in teens and young adults. The M:F ratio is 2:1. Radiographically, a well-defined uni-/multilocular radiolucency containing variable amounts of radiopaque material (either denticles or a central, solid mass) is seen. Growth characteristics, management and prognosis are similar to SMA.

Calcifying cystic odontogenic tumour (CCOT, keratinizing and calcifying odontogenic cyst, calcifying odontogenic cyst, Gorlin cyst)

This is a rare cystic benign neoplasm,[81, 83] occurring mainly in the anterior region of either jaw, over a wide age range and without sex predilection. Most cases are asymptomatic and present radiographically as a well-circumscribed unilocular radiolucency containing variably-sized calcified bodies. Adjacent erupted teeth frequently show root resorption or divergence and unerupted teeth may be displaced. Histologically, the cyst shows similarities with UA but the stellate-reticulum-like cells are transformed to eosinophilic ghost cells. Ghost cells frequently calcify and dentinoid-like material may be deposited within the fibrous cyst wall. Enucleation is usually curative and recurrence is rare.

Dentinogenic ghost cell tumour (calcifying ghost cell odontogenic tumour, odontogenic ghost cell tumour) (DGCT)

This tumour[81, 84] used to be considered a solid variant of the calcifying odontogenic cyst but is now classified as a locally invasive neoplasm with features resembling ameloblastoma but characterized by keratinization, ghost cells and dentinoid.[50] The tumour occurs in any tooth-bearing area of either jaw (but mainly premolar), affecting a wide age range with males more frequently affected than females. Small lesions are generally asymptomatic but larger lesions cause bony expansion or perforation, and tooth displacement and mobility. Radiographically, the lesion is generally well demarcated, radiolucent or mixed radiolucent/radiopaque. Histologically, an infiltrative margin is seen and the presence of ghost cells and dentinoid are critical in distinguishing the lesion from an ameloblastoma. Distinction from a CCOT can be difficult. The presence of mitoses is suspicious of transformation to odontogenic ghost cell carcinoma. The infiltrative nature of DGCT dictates wide local excision as the treatment of choice.

Odontogenic fibroma

Controversy exists over the concept and definition of this rare tumour.[85, 86] Currently, odontogenic fibroma (OF) is applied to two histological types:[50] epithelium-poor (formerly known as simple type) and possibly derived from dental follicle, and epithelium-rich (formerly known as complex or WHO type) and possibly derived from periodontal ligament. The intraosseous lesion, most common in the premolar region of the mandible, is mainly epithelial-rich and affects adults with a M:F ratio of 1:3. The usual presentation is a slow-growing, painless jaw swelling with cortical expansion. Radiographically, most cases present as a unilocular radiolucency with a well-defined sclerotic border. Larger lesions may have a scalloped margin and sometimes, spotted radiopacities are evident. Histologically, the epithelial-rich type is composed of cellular, fibroblastic connective tissue containing islands and strands of inactive-looking odontogenic epithelium and foci of calcified material (metaplastic cementum/osteoid/dentine). Differential diagnosis includes hyperplastic/enlarged dental follicle and fibromyxoma. OF is well circumscribed and simple enucleation is curative.

Odontogenic myxoma (OM), odontogenic fibromyxoma (OFM)

This benign, locally infiltrative tumour[87, 88] accounts for 3% of odontogenic neoplasms. Pathogenesis is uncertain and the name was originally based on location, resemblance to dental papilla/follicle, and sporadic presence of odontogenic epithelium. Ultrastructural and immunohistochemical studies have not confirmed an origin from ectomesenchyme of the developing tooth and suggest a non-odontogenic origin from myofibroblasts and/or histiocytes. The tumour is more common in females, typically 15–35 years, and two-thirds occur in the mandible (mainly posterior). Typical presentation is a slowly increasing, painless swelling or asymmetry of the affected jaw but growth may be rapid and associated with tooth mobility, root resorption, and in maxillary lesions, nasal obstruction and exophthalmus. Radiographically, a multilocular, soap-bubble (honeycomb) appearance is seen (as in ameloblastoma, KCOT and haemangioma). Macroscopically, the cut surface is white, mucoid and sticky. Histologically, tumour infiltrates bone marrow spaces and consists of cytologically bland rounded, spindle-shaped or angular cells evenly spaced within abundant mucinous matrix. The matrix is finely fibrillar and may contain scattered small islands of odontogenic epithelium, sometimes with a hyaline cuff. More collagenous examples are designated fibromyxoma. The differential diagnosis includes enlarged (hyperplastic) dental follicle, and myxomatous degeneration in fast growing neoplasms such as chondrosarcoma and liposarcoma. Recurrence ranges from 10% to 33% and is more common after conservative surgery. Currettage with frozen-section assessment of margins is generally adequate for smaller lesions but radical resection may be necessary for large, diffuse lesions. Metastases do not occur.

Benign cementoblastoma

This is a benign neoplasm[89, 90] arises from cementoblasts and is fused to a tooth root. The mandibular first molar in young adults (peak, 20 years of age) is most frequently affected. There is no sex predilection. Most present with painful swelling of the buccal and lingual alveolar ridge over a vital tooth. Radiographically, a well-defined, rounded, radiopaque or mixed-density lesion, replacing the apical third of the root, is surrounded by a narrow radiolucent zone (**Figure 25.19**). Histologically, dense

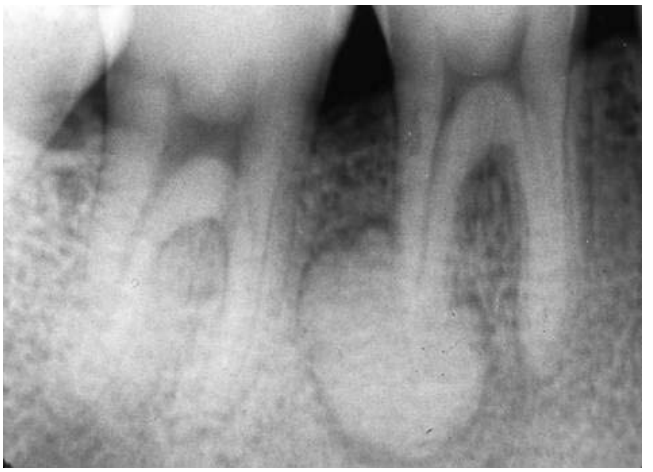

Figure 25.19 Periapical radiograph of benign cementoblastoma, typical relationship to root of molar tooth, radiodense with lucent rim.

masses of acellular cementum (similar to Pagetoid bone) are supported by a fibrovascular stroma often with scattered multinucleated cells. A zone of unmineralized cementoid is seen peripherally. The dental origin is key to distinguishing it from an osteoblastoma and osteosarcoma. Extraction of the associated tooth and complete enucleation are recommended. Recurrence is common after incomplete removal.

MALIGNANT ODONTOGENIC TUMOURS

These are rare.[50] Some appear to be the malignant counterparts of benign odontogenic tumours. Others arise by malignant transformation of epithelial residues or the lining of odontogenic cysts. Aetiology is unknown. Odontogenic carcinomas[91] are more frequent in the elderly while odontogenic sarcomas affect younger age groups. Clinical features include swelling, pain, bleeding, mucosal ulceration, tooth mobility, paraesthesia, and pathological fracture. Radiographically, extensive jaw destruction with ill-defined borders, sometimes with patchy radiopacities, is typical. In carcinomas, metastasis to local lymph nodes and distant sites may occur early and prognosis is generally poor even after resection with tumour-free margins.

Metastasizing (malignant) ameloblastoma

This is a diagnosis made retrospectively when a histologically typical ameloblastoma gives rise to metastases (mainly lung).[92]

Ameloblastic carcinoma (primary type)

This rare tumour, an ameloblastoma with atypia,[92] presents mainly in the posterior mandible and shows no obvious sex predilection. Differential diagnosis includes ameloblastomas with occasional mitotic figures (and no other cellular/architectural atypia), other odontogenic carcinomas and metastatic carcinoma. Pulmonary metastases are present at initial diagnosis in around one-third of maxillary lesions but mainly follow local recurrence in mandibular lesions.

Ameloblastic carcinoma, secondary type (de-differentiated)

This very rare lesion arises within a pre-existing, and often long standing/recurrent, benign ameloblastoma.[92] Cellular atypia and nerve invasion are characteristic changes. Size and proximity to skull base and other vital structures dictate the adequacy of surgical resection and survival.

Primary intra-osseous squamous cell carcinoma (primary intra-osseous epidermoid carcinoma)

This is a central jaw carcinoma derived from odontogenic epithelial residues.[93] Once the tumour destroys the cortex, it may merge with the surface mucosa and be difficult to distinguish from squamous cell carcinoma (SCC) of mucosal (and antral) origin.

Primary intra-osseous squamous cell carcinoma (PIOSCC), **solid type,**[94] invades marrow spaces and induces osseous resorption. The aetiology is unknown. It is derived from odontogenic epithelial residues such as the periradicular rests of Malassez within the periodontal ligament and the reduced enamel epithelium surrounding impacted unerupted teeth. Dedifferentiation from a benign ameloblastoma is a further (rare) possibility. Most arise in later adult life with a M:F ratio of 2:1). Most are located in the body and posterior mandible. Maxillary cases tend to involve the anterior region. The lesion is often discovered as an incidental irregular, non-corticated radiolucency following routine jaw radiography. Large lesions may cause facial swelling and paraesthesia. Histologically, PIOSCC, solid type, is generally moderately differentiated and without specific features. Metastatic SCC must be excluded by clinical and radiological examination. Surgical resection is frequently followed by local recurrence, regional and distant metastases and prognosis is poor.

The other rare subtypes of **PIOSCC**, derived from **KCOT**,[94, 95] and **PIOSS**, derived from **odontogenic cysts**,[94] show SCC in association with a KCOT or odontogenic cyst and generally affect older adults, with a M:F ratio of 2:1. The mandible is much more affected than the maxilla. The SCC may be discovered on histological assessment of a suspected benign tumour/cyst or may present with pain, swelling, loose teeth, non-healing tooth socket, paraesthesia and regional lymphadenopathy. Radiographic appearances range from a typical cyst to an ill-defined radiolucency to gross cortical destruction and soft-tissue extension. Histologically, well differentiated SCC is seen merging with KCOT or the lining of the odontogenic cyst which may show dysplasia or features of verrucous hyperplasia/carcinoma. Differential diagnosis[93] can include keratoameloblastoma, SOT, central mucoepidermoid carcinoma and metastatic tumour. Based on small numbers,

the prognosis is thought to be more favourable than PIOSCC, solid type.

Clear cell odontogenic carcinoma

The rare clear cell odontogenic carcinoma (CCOC)[95–97] predominantly affects the mandible of older females, presenting as jaw swelling with loosening of teeth and radiographically, as an ill-defined radiolucency with root resorption. Histologically, a biphasic pattern of sheets of clear cells and irregular cords of basaloid cells supported by fibrous septae is typical. Many of the tumour cells contain diastase-degradable PAS-positive granules. Differential diagnosis includes salivary gland neoplasms, clear cell variant of CEOT, metastatic renal cell carcinoma and malignant melanoma. Surgical resection may be followed by local recurrence, regional and distant (lungs, bone) metastases and prognosis is poor for large lesions. Post-operative radiotherapy should be considered especially if there is cortical erosion/perforation.

Ghost cell odontogenic carcinoma

This rare neoplasm[81, 98] shows features of CCOT and/or GCOT and mainly affects the maxilla in adult males. Clinical symptoms include swelling and paraesthesia. Radiographically, a poorly demarcated radiolucency with patchy radiopacity and root displacement or resorption is typical. Histologically, the malignant component consists of rounded, mitotically active, epithelial islands in a fibrous stroma and lies adjacent to, or admixed with, typical benign GCOT. Prognosis is unpredictable. Some recur locally and metastasize.

Ameloblastic fibrosarcoma, fibro-dentinosarcoma and fibro-odontosarcoma

Ameloblastic fibrosarcoma (AFS) is the initial diagnosis in around two-thirds of cases while the remainder develop within a pre-existing AF.[99] AFS[100] has a mean age of 28 years (compared to 15 years for AF) and M:F ratio of 1.6:1. Posterior mandible is the most common site. Histologically, benign epithelial nests and cords are present in a highly cellular, cytologically malignant ectomesenchyme. Scattered areas of dentine and enamel, dentine and cementum are present in the ameloblastic fibro-dentinosarcoma (AFDS) and fibro-odontosarcoma (AOFS),[100] respectively. Surgical resection is treatment of choice and the tumours are generally low grade, and with few metastases and a better survival than other jaw sarcomata.

INTRA-OSSEOUS SALIVARY GLAND TUMOURS

Salivary-type carcinomas may occur in the jaws as primary central tumours,[101] but this is very rare compared to the more common jaw involvement by direct spread from an extra-osseous site (mainly, parotid or retromolar). Mandible is affected more often than maxilla and mucoepidermoid and adenoid cystic carcinoma are the most common histological types. Intra-osseous salivary tissue may result from entrapment during embryonic development, surgical manipulation, or metaplastic odontogenic epithelium.[100] Central intra-osseus salivary adenocarcinoma with non-specific/not otherwise specified histology, is very rare and imaging and monitoring clinical progress are important adjuncts to immunohistochemistry in reaching the correct diagnosis. Intra-osseous salivary gland tumours (IOSGT) are usually managed by radical surgical excision, often supplemented by radiotherapy.

MISCELLANEOUS NEOPLASMS

Ewing sarcoma

This is rare in the jaws, mainly affecting the mandibular body in children and young adults.[102] Progressive bone swelling, followed by pain, loosening of teeth and mucosal ulceration is usual. Systemic symptoms of fever, leucocytosis, raised ESR and anaemia indicate a poor prognosis. Histologically, the neuroectodermal Ewing sarcoma cells resemble enlarged lymphocytes and form sheets separated by fibrous septae. Wide excision, followed by radiotherapy and combination chemotherapy, is the usual treatment but may be unsuccessful due to distant spread to the lungs, other bones and lymph nodes.

Haemangioma of bone

Haemangioma of the jaws is uncommon.[34, 79, 103] Solitary lesions mainly affect the mandible, and females, but involvement of the maxilla is an important part of Sturge–Weber syndrome (together with facial port-wine stain and epilepsy). Progressive, painless swelling is the usual presentation. Pulsation indicating resorption of the overlying bone, and loosening teeth with gingival bleeding may be seen with larger lesions. Radiographically, the honeycomb locularity can be difficult to distinguish from ameloblastoma, KCOT and OM. Fresh blood on attempted aspiration is an important diagnostic clue. Histologically, most intra-osseous haemangiomas are of cavernous type. Wide surgical resection may be the only practical treatment but selective arterial embolization may be useful if there are well-defined feeder vessels.

Melanotic neuroectodermal tumour of infancy (Progonoma)

This is a rare tumour of neural crest origin that involves the anterior maxilla either congenitally or in the first few months after birth.[76, 79, 104] It presents as a painless, bluish swelling which occasionally grows rapidly. Radiographically, there is ragged bone destruction and displacement of developing teeth. Histology shows the characteristic clusters and strands of melanin-pigmented and non-pigmented epithelial cells supported by a fibrous stroma. The tumour is benign but non-encapsulated.

Curettage or conservative surgery is curative and recurrence is rare.

Multiple myeloma (myelomatosis), solitary plasmacytoma

Multiple myeloma, a monoclonal immunoglobulin-producing neoplasm of plasma cells, may present with multiple 'punched-out' radiolucencies (typically of the skull vault and areas of red-marrow) on routine radiography or with bone pain/tenderness or signs of bone marrow replacement (anaemia, infections and thrombocytopenia).[34, 79, 105] Peak incidence is 50–70 years of age. Histologically, sheets of neoplastic plasma cells may be well or poorly differentiated with bi- and multi-nucleated forms. Immunohistochemistry for kappa and lambda chains and Ig class shows the monoclonal nature and monoclonal 'M' band seen on serum electrophoresis is confirmatory. Healing may follow combination chemotherapy but relapse is common and 5-year survival is only 20%. The solitary plasmacytoma[106] is managed by radiotherapy and has a good 5-year prognosis but the majority of patients succumb to multifocal disease after 10 or more years.

Langerhans cell histiocytosis (histiocytosis X), eosinophilic granuloma

Langerhans cells, the antigen-presenting histiocytes of epithelia, occasionally give rise to bone tumours. Langerhans cell histiocytosis (histiocytosis X) (LCH) of bone may present as a single 'eosinophilic granuloma'; or multifocally within bone and other organs, or with generalized disseminated multiorgan disease.[34, 79, 107] Multifocal involvement of the craniofacial bones, orbit and posterior pituitary presents with skull defects, exophthalmus and diabetes insipidus (Hand-Schuller-Christian syndrome). The most severe form, disseminated Letterer–Siwe disease, occurs mainly in infants and has a high mortality. Unifocal and multifocal eosinophilic granuloma typically occur in older children/young adults with a 2:1 M:F ratio. The cranium and jaws, in particular the mandible, are common sites. Radiographically, the lesions are osteolytic, rounded and indistinct. Multiple jaw lesions result in the classic 'teeth floating in air' appearance. Loosening and exfoliation of teeth is a common presentation. Involvement of the temporal bone can present as otitis media mastoiditis. Histologically, collections of histiocytes admixed with eosinophils are seen. Immunohistochemical demonstration of the Langerhans cells surface antigen, CD1a, and S-100 protein is diagnostic and has largely replaced the electron microscopical detection of Birbeck granules. Generally, eosinophilic granuloma heals after curettage and some regress spontaneously. More disseminated disease is unpredictable. Genetic studies have shown LCH represents a clonal proliferation and the neoplasm may progress despite irradiation and/or chemotherapy.[107]

METASTATIC TUMOURS

Metastatic carcinoma to the jaws may be from a known or as yet undiagnosed primary carcinoma.[48, 106, 142] Elderly men and women are mainly affected and haemopoietic marrow within the posterior mandible is the most commonly involved site. It is not known whether healing extraction sockets and/or subclinical chronic inflammation which result in foci of increased vascularity encourage deposition of metastatic tumour at other sites within the jaws. Clinical presentation varies from asymptomatic to mobile/drifting teeth, pain, swelling and pathological fracture. Radiography typically reveals an ill-defined or mottled radiolucency. For men, the most common origins of the primary carcinoma are lung, prostate and adrenal glands; and for women, breast, adrenal glands, colon and rectum, genital tract and thyroid.

Details of the immunohistological profiles for the cytokeratins and transcription factors that are useful in the histological diagnosis of the source of the metastatic carcinoma, and the limitations, are discussed by Woolgar et al[102] A logical approach to identify an undifferentiated/poorly differentiated neoplasm begins with a basic screening panel including markers for epithelial, mesenchymal and haemopoietic lineages, and malignant melanoma. This is then followed by staining for cytokeratin profiles and specific antigens or transcription factors (useful in poorly differentiated neoplasms) and in suspected adenocarcinomas, mucosubstance histochemistry. Limited confirmatory staining only is necessary if the existence of a primary tumour is already known and declared on the pathology request form. Management is palliative and depends on factors related to the primary tumour, number and site of metastatic deposits and general patient factors. Even when the prognosis and life expectancy are poor, localized radiotherapy can help control symptoms such as jaw pain particularly when referred to the ear.

KEY POINTS

- The bones of the facial skeleton, by virtue of their association with dentition, can be the origin of a unique group of bone cysts and tumours.
- Owing to the complex embryologic origin, significant epithelial remnants can be trapped within the jaw bones, leading to the high prevalence of cysts in the human body.
- Additionally, other osseous benign and malignant pathology seen elsewhere in the body, can also arise in the jaw bones.
- While clinical presentation and radiologic findings may indicate the nature of the pathology, histologic examination is almost always required to make the diagnosis owing to the wide array of pathologic processes.
- Specialist pathologic expertise is needed as some of the entities are rare and the classification of these lesions is constantly evolving.
- Malignant and systemic diseases affecting the jaw bones will need the input of a multidisciplinary team.

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CHAPTER 26

HEAD AND NECK PATHOLOGY

Ram Moorthy, Adrian T. Warfield and Max Robinson

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SEARCH STRATEGY

Data in this chapter may be updated by a PubMed search using the keywords: head and neck, biopsy, pathology, cytology, histopathology, histochemistry, immunohistochemistry, *in situ* hybridization, tumour, neoplasia, salivary gland tumour, squamous cell carcinoma, nasopharyngeal carcinoma, lymphoma and neuroectodermal tumour.

INTRODUCTION

The head and neck comprises a complex anatomical region composed of diverse tissues. Consequently many of the diseases that occur are challenging to diagnose and require careful clinico-pathological correlation. Some of the diseases are unique to the site and specialist knowledge is required to derive a differential diagnosis and pursue the appropriate investigations leading to a definitive diagnosis and effective management. Furthermore, some of the diseases are rare and require evaluation by specialist pathologists with the requisite experience to render an accurate diagnosis.

For neoplastic disease, the pathologist has a significant role in assessing whether the tumour has been completely eradicated. For malignant disease, parameters such as tumour grade and stage are important prognostic indicators and determine adjuvant treatment. Furthermore, the evolution of molecular pathology in recent years has led to the emergence of tests that can be used to tailor treatment for individual patients. Biological treatments, such as trastuzumab for breast cancer, require 'companion diagnostic tests' to select the right patients. This strategy ensures that patients have access to the most effective treatment and the best chance of cure. Whilst targeted treatments for head and neck disease remain elusive, this is likely to change over the next decade.

PATHOLOGICAL EVALUATION

There are a number of techniques available to obtain a biopsy specimen for pathological evaluation. The choice of technique mainly depends on the size and location of the lesion (**Table 26.1**).

Fine-needle aspiration biopsy

Fine-needle aspiration biopsy (FNAB) is the first-line investigation for patients presenting with cervical lymphadenopathy or with a lesion in the major salivary glands or thyroid gland.[1] FNAB is highly accurate, especially when the evaluation is restricted to determining non-neoplastic vs. neoplastic and benign vs. malignant.[2] Furthermore, the procedure is acceptable to patients and there is minimal morbidity. The technique is simple to perform and relatively inexpensive. FNAB can be performed 'free-hand' by palpation; however, the use of ultrasound guidance increases the yield of relevant material. It may be possible to get support from a cytologist to determine the adequacy of the specimen in the clinic. Some units provide a 'one-stop' head and neck lump clinic with immediate cytological diagnosis.[3] It is important to emphasize that a negative result on FNAB does not exclude disease and that 'triple assessment' (clinical, imaging and cytolopathology) is essential to arrive at the correct diagnosis.

Fixed smears should be immersed in fixative, usually alcohol-based, without delay and are typically stained with the Papanicolau (Pap) method or sometimes haematoxylin and eosin (H&E). Air-dried smears are best subjected to assisted air flow and are usually stained with a Romanowsky-type stain, commonly May-Grünwald-Giemsa (MGG) or Diff-Quik variants (**Figure 26.1**). Needles and syringe

TABLE 26.1 The advantages and disadvantages of commonly used tissue sampling techniques

Type of sample	Advantages	Disadvantages
Fine-needle aspiration biopsy (FNAB)	• Simple technique • Inexpensive • Can be undertaken in clinic • Relatively risk free • Does not usually compromise future management • Highly accurate, especially when the evaluation is restricted to determining non-neoplastic vs. neoplastic and benign vs. malignant	• Primary cytological diagnosis by FNAB must be confirmed by histology prior to radical treatment for head and neck cancer • Diagnostic yield is both lesion-sensitive and operator-dependent and there can be a high non-diagnostic rate, but this may be improved with the use of ultrasound guidance • Requires an expert cytopathologist • Clinicians must be aware of inherent limitations including a risk of false positives and false negatives • FNAB is of limited help in the diagnosis of lymphoma. Flow cytometry may be helpful in excluding a diagnosis of lymphoma
Core biopsy	• Simple technique • Inexpensive • Can be undertaken in clinic • The diagnostic yield is higher than for FNAB and the sample undergoes histopathological analysis, and therefore specific cytopathological expertise is not required • The complications of the procedure are relatively minor, the most common being haematoma formation • By contrast to FNAB, a core biopsy sample permits a greater chance of sub-classification of a lymphoma and may obviate the need for an open biopsy	• Appropriate precautions are required for patients taking anticoagulation therapy to prevent bleeding and haematoma formation • There is a theoretical risk of tumour seeding associated with the larger needles used in obtaining a core biopsy, but published case series have rarely encountered this complication
Incision biopsy	• Can provide definitive histological diagnosis	• Can affect definitive management of the tumour • Can require admission as a day case • May require a general anaesthetic • Higher complication rate than FNAB or core biopsy • Costlier than FNAB or core biopsy
Excision biopsy	• Can provide definitive histological diagnosis • Can be definitive treatment of the tumour	• Higher risk of complication compared to other biopsy techniques • Can require admission • May require a general anaesthetic • Costliest method of obtaining a biopsy

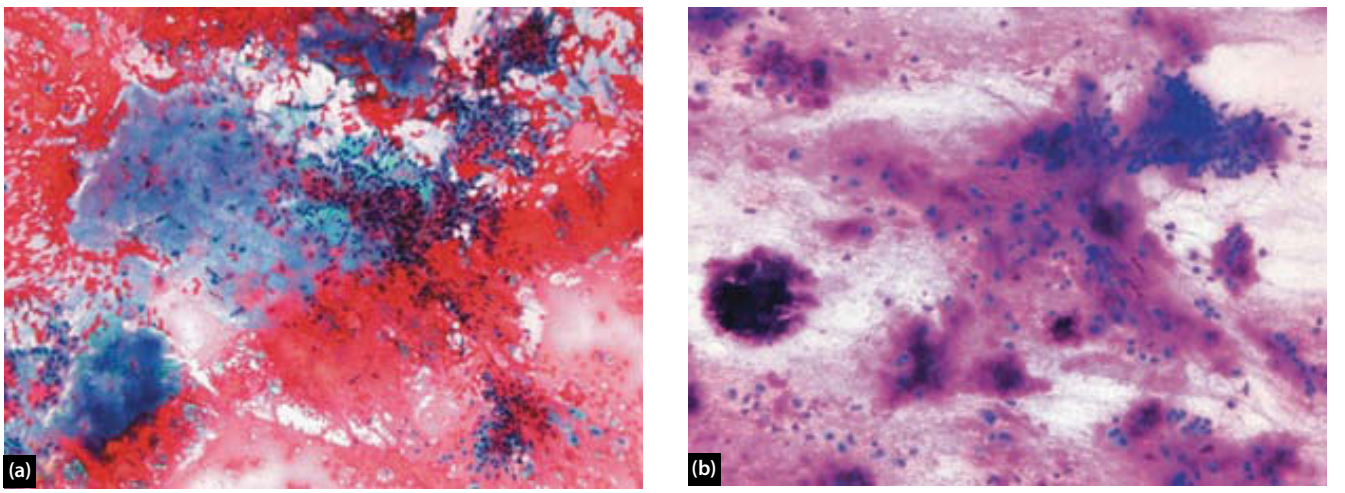


Figure 26.1 Fine-needle aspiration biopsy (FNAB) preparations from a pleomorphic salivary adenoma. (a) This alcohol-fixed slide shows weakly stained, feathery stroma admixed with loosely cohesive, isomorphic epithelioid and spindle cells (Pap stain, medium magnification). **(b)** This air-dried slide from the same tumour at the same magnification highlights the intensely stained myxoid ground substance, which obscures cytological detail in areas (May-Grünwald-Giemsa (MGG) stain, medium magnification).

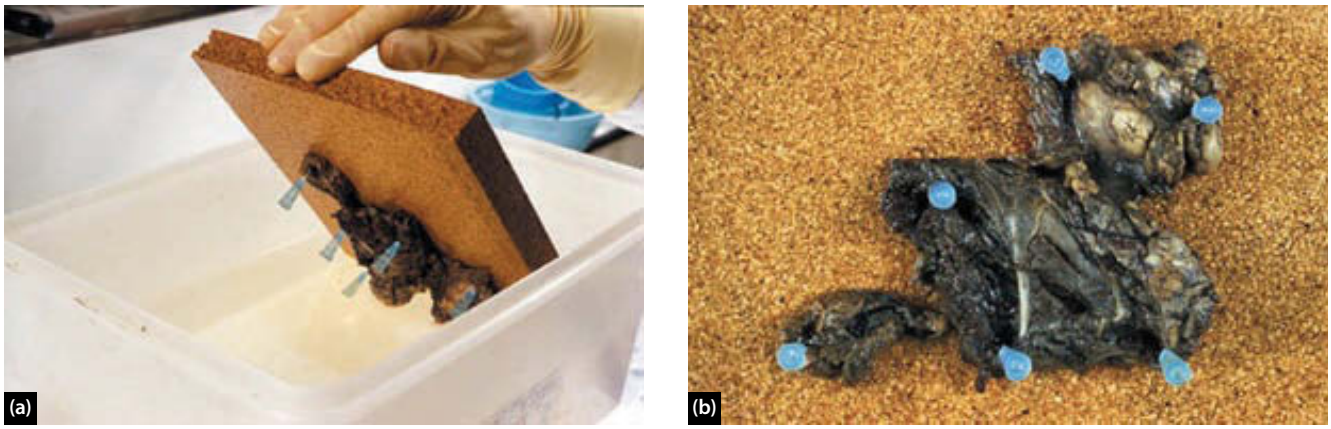


Figure 26.2 Resection specimen orientation utilizing a corkboard. **(a)** Radical neck dissection specimen pinned to cork block, inverted and immersed to float in formalin. **(b)** The fixed specimen as received in the laboratory, ready for trimming and block selection. This was accompanied by separate annotation by the surgeon. Alternatively, the surgeon may prefer to separate the levels in theatre and place them individually in labelled pots.

hubs may be rinsed in transport medium or proprietary liquid-based cytology fluid (e.g. SurePath, BD or, ThinPrep, Hologic) in an attempt to maximize the cell yield. The resultant 'needle washings' may be handled in the laboratory, by a variety of cell concentration techniques, such as filtration or centrifugation dependent upon local preferences and the reliance upon liquid-based cytology. Any clot material is best processed using conventional histology, because free-floating cells tend to be sequestered in such clots and valuable material may otherwise be discarded.

Core biopsy

A core biopsy is performed using a specific large calibre needle (e.g. Tru-Cut, BD) and will yield a cylinder of tissue that can undergo histological analysis. The clinical utility of a core biopsy is limited by the requirement for local anaesthesia, patient discomfort and the risk of damage to local structures.[4] The use of ultrasound guidance reduces the risk of inadvertent damage to a large calibre blood vessel.[5] The amount of tissue harvested and the preserved tissue architecture increases the diagnostic utility and there is also the possibility of yielding sufficient material for immunohistochemical analysis. It is particularly useful for metastatic disease, where the primary tumour location is unknown. In these circumstances, immunohistochemical tests can be used to indicate the most likely anatomic site of the primary tumour.

Incision biopsy

Incision biopsy involves taking a representative sample or wedge of a lesion for histological analysis. This is a suitable technique for obtaining a diagnosis in accessible tumours affecting the oral cavity, pharynx, larynx or hypopharynx. However, in lesions affecting the major salivary glands or in cervical lymphadenopathy, incision biopsy may compromise further treatment so is used as a last resort.

A sufficient sample of tissue must be obtained to allow histopathological analysis. Thermal artefact and mechanical disruption, either crushing or stretching, during handling or processing of the specimen can make analysis difficult and occasionally impossible. Certain tissues (e.g. lymphoid tissue) and tumours (e.g. neuroendocrine carcinoma) are more susceptible to this than others. It must be noted that a thick biopsy does not necessarily equate to a deep biopsy; it is often the interface between the lesion and the underlying connective tissue that is critical when seeking evidence of invasion and a thick sample from an exophytic epithelial proliferation may still be too superficial to adequately assess this feature.

Excision biopsy

Excision biopsy involves complete removal of the lesion and provides a definitive histological diagnosis. This can range from the removal of a small vocal cord polyp to a major *en bloc* resection. Where appropriate, the specimen should be orientated by the surgeon using sutures or marker clips in appropriate positions. Annotated diagrams or digital photographs aid communication. Specimens can be pinned or clipped on to a cork board or a foam sheet (**Figure 26.2**). Dehydrated cucumber slices are a suitable medium for laryngeal biopsies, which are held in place with tissue adhesive (**Figure 26.3**).[6] Resection planes or other structures of particular clinical concern ought to be brought to the pathologist's attention, especially if these may not be immediately obvious following inevitable distortion induced by fixation. It should always be borne in mind that there will be a reduction in measured specimen margins when a fixed, processed, stained and mounted tissue section is compared to the intra-operative state due to shrinkage inherent in tissue preparation for microscopic examination.

Sentinel lymph node biopsy

This technique is recommended for patients with clinically T1/T2 N0 oral cavity squamous cell carcinoma.[7]

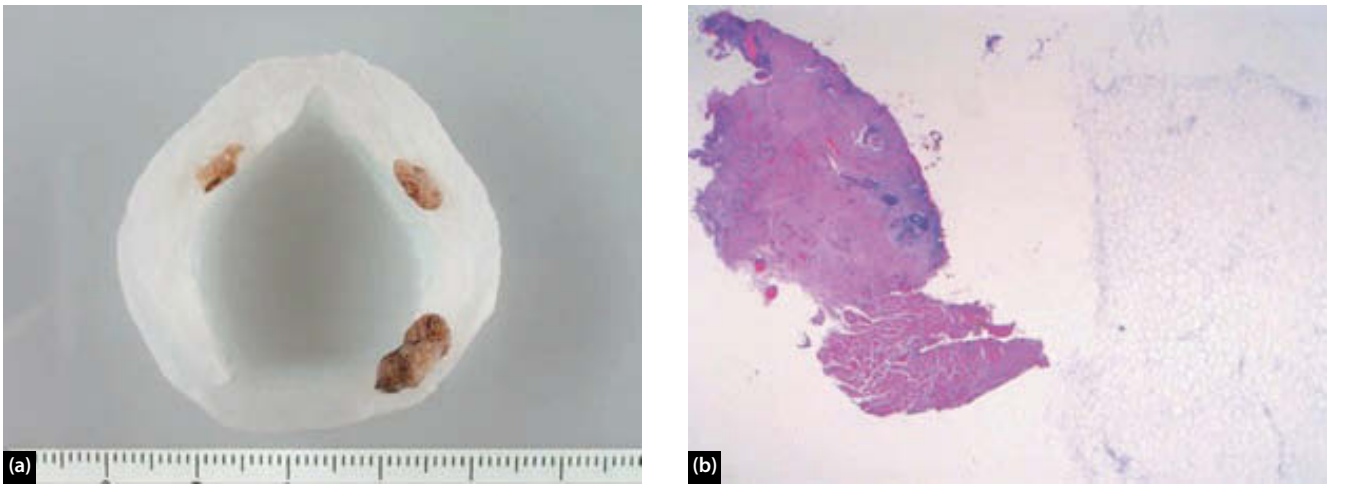


Figure 26.3 Biopsy orientation using a biomount. **(a)** Three laryngoscopic biopsies glued to a dehydrated cucumber biomount in order to maintain correct orientation in the laboratory. An accompanying endoscopic digital photograph further assists handling of such small biopsies. These may be further inked and/or sliced prior to processing. **(b)** A correctly embedded, though heavily thermalized, laryngeal biopsy on the left with anucleate cucumber biomount to the right (H&E stain, ultralow magnification).

Prior to surgery, four sites around the oral carcinoma are injected with a radioactive-labelled colloid tracer. The tracer enters the lymphatic system and drains to the first echelon lymph nodes. The radioactive lymph nodes can then be mapped by imaging. The surgeon uses a gamma radiation detection system to confirm the location of the sentinel lymph nodes and harvests them using a small incision in the neck. Up to four sentinel nodes may be found. Each 'hot node' is then processed in the pathology laboratory using a protocol that samples the entire lymph node at 125 µm intervals. Immunohistochemical staining for cytokeratins (pan-cytokeratin cocktail, AE1/AE3) is used to increase the sensitivity of the test. A negative sentinel lymph node biopsy has a high negative predictive value (95%) and the neck can be monitored, avoiding elective neck dissection. A positive lymph node requires a completion neck dissection, which is performed at a second operation.

Request form

When requesting pathological analysis of a specimen, it is vital that the pathologist is provided with all relevant information to enable a full assessment of the specimen. Ideally the information should include:

- patient identification and demographics
- clinician responsible
- relevant details of lesion (duration, symptoms, etc.)
- clinical photographs of the lesion can also help
- differential diagnoses
- relevant medical history and medications
- history of tobacco, alcohol and drug use
- previous treatment surgery and/or radiotherapy
- type of biopsy (FNAB, core biopsy, incision biopsy or excision biopsy)
- site of biopsy (if biopsies are taken from multiple sites, each site should be clearly labelled and allocated a separate specimen pot).

If the specimen has been orientated, then an annotated diagram or photograph should be included with the request.

Tissue preparation

Tissue specimens are ideally fixed immediately in theatre by immersion in 10% neutral buffered formalin (NBF), which is the routine fixative of choice. This effectively stops metabolism and arrests autolysis and putrefaction, thereby preserving the tissue structure. The apocryphal maxim is that the minimum ratio by volume of NBF to specimen should be 10 to 1, although this is somewhat arbitrary and if this was ever evidence-based, it is likely to be influenced by intangible factors, such as type of tissue, temperature, agitation and so on – as a rule, more liberal volumes of fixative are preferable. On rare occasions, alternative fixatives, such as glutaraldehyde or alcohol, may be employed if specialized studies (e.g electron microscopy) are required. Fresh unfixed material intended for intra-operative frozen section examination, direct immunofluorescence, molecular studies or microbiology must be despatched without delay to the laboratory, cognizant that it constitutes a biohazard.

Upon receipt in the laboratory, the specimen identity is corroborated and a unique accession number is allocated. Following an appropriate period of fixation (24–48 hours), either the pathologist or senior biomedical scientist staff will describe the specimen macroscopically, and dissect and submit representative tissue slices for examination. These slices are inserted into proprietary sealable cassettes appropriately labelled.

After a further period of fixation, the tissue slices undergo cycles of dehydration, clearing, infiltration and embedding in preparation for microtomy (section cutting). During dehydration, alcohol replaces the aqueous fixative within the tissue. Clearing replaces the alcohol with an antemedium, such as xylene. Molten paraffin wax then replaces the clearing agent and infiltrates the tissue. The tissue is

subsequently embedded by encapsulation in paraffin wax in a mould to provide a rigid support for microtomy. The additional step of decalcification may be instituted in mineralized tissue, which might otherwise hinder sectioning. Automatic tissue processors enhanced by pressure, vacuum, heat and microwave facilities in a self-contained, microprocessor-controlled, programmable unit are used in many modern laboratories, tailored to local conditions.

The pre-chilled, hardened paraffin wax-embedded tissue block is then sliced, typically at 3–5 µm thick on a microtome. The thin sections are then floated on a warm water bath prior to transfer on to a glass slide. The sections are then dried on a hotplate.

The sections may now be stained, typically with H&E and mounted under a glass or self-adhesive plastic film coverslip to form a permanent preparation. Haematoxylin stains nuclei dark blue and tissue glycoproteins light blue. Eosin stains the cytoplasm and collagen pink. The H&E stained slides are then made available to the pathologist for examination. A wide repertoire of additional histochemical and/or immunohistochemical stains may be required, on additional sections, to render a diagnosis. The majority of biopsies are reported within 7 days; however, it is possible to reduce the 'turn-around time' for urgent specimens to 24 hours. Large resection specimens that include bone require a decalcification step, which extends the processing time to around 2 weeks.

Histochemistry

Histochemistry is used to highlight a variety of biological substances in the tissue. Sometimes referred to as 'special stains', there are numerous methods based on chemical reactions that can be visualized by a specific colour change in the tissue sections. For example, Periodic acid-Schiff (PAS) stain can be used to highlight carbohydrates, which stain deep purple; pre-treatment of the tissue section with the enzyme diastase removes simple carbohydrate moieties leaving mucins, which are found in glandular secretions and fungal hyphae. Elastic van Gieson stain is used to appreciate tissue architecture, especially blood vessels; elastin fibres stain black and collagen red. Ziehl Neelsen stain is used to detect bacteria and identify acid-fast bacilli in tuberculosis.

Immunohistochemistry

The principle underpinning immunohistochemistry (IHC) is the demonstration of an epitope or antigen via its binding to a specific antibody, which in turn is conjugated to a label that can be visualized by microscopy. A variety of reporter and linkage systems to produce a visual signal have been developed based on fluorescent molecules and enzyme-generated chromogenic substrates.

In general, monoclonal antibodies are more specific than their polyclonal counterparts. Importantly, no antibody is 100% sensitive and specific – immunophenotyping is best performed using a panel of expected positive and negative antibodies. Expected staining can be checked by examining 'internal controls' (tissue elements that are positive for the antibody) and 'external controls' ('on slide' analyte control material such as cell lines or tissue/tumours with known protein expression patterns). It is important to be mindful of aberrant cross-reactivity, spurious co-expression, false positives, false negatives and vagaries of technical quality. Correlation with conventional morphology is imperative.

Among the broad categories of commercially available diagnostic markers are antibodies directed against intermediate filaments (e.g. cytokeratins, desmin, neurofilament, vimentin), epithelial markers (e.g. Ber EP4, epithelial membrane antigen), structural proteins (e.g. calponin), storage granules/products (e.g. calcitonin, chromogranin, synaptophysin, thyroglobulin), hormone receptors (e.g. oestrogen, progesterone), nuclear epitopes (e.g. p16, thyroid transcription factor-1), lympho-reticular epitopes (e.g. CD3, CD20, CD79a), cell proliferation (e.g. Ki67), apoptosis molecules (e.g. bcl-2, p53) and infectious agents (e.g. cytomegalovirus, herpes simplex virus 1/2, human herpes virus 8, varicella zoster, LMP-1 for Epstein–Barr virus (EBV)).

In-situ hybridization

In-situ hybridization (ISH) is similar to IHC, but instead of using antibodies to detect a protein, a DNA probe is designed to hybridize (stick) to either a complementary sequence of RNA or DNA. RNA ISH is used to detect EBV and kappa and lambda light chains in B lymphocytes. DNA ISH can be used to identify low-risk and high-risk human papillomavirus infection. Chromosomal abnormalities, such as amplifications, translocations and deletions, can be identified by fluorescence ISH.

Molecular tests

More recently, molecular biology techniques have been used to generate high resolution genetic profiling of tumours, by either DNA sequencing and/or gene expression arrays. Such molecular information is currently used in the management of breast cancer (e.g. Oncotype DX breast cancer test). It is likely that these types of test will become available for head and neck cancers in the not too distant future. Projects like the US Cancer Genome Atlas (TCGA) aim to accelerate the understanding of the molecular basis of cancer and facilitate molecular diagnosis.[8] One of the aims of the 100 000 genomes project (Genomics England) is to create a new genomic medicine service for the National Health Service for the benefit of patients.[9]

Multidisciplinary diagnosis

The cytological and histopathological analysis is a complex process. It cannot be overemphasized that reaching a final conclusion depends on many factors, including detailed site-specific knowledge coupled with experience of normality, familiarity with the manifold appearances of many disease processes at various stages in their natural history, awareness of mimics and artefacts plus cognizance of the limitations of the technique, in conjunction with patient-specific details and the clinical context.

Without consideration of these and appropriate correlation with clinical, radiological and other relevant background information, a pathological slide is in danger of becoming a two-dimensional, brightly stained artefact, which may be as misleading as it can be potentially helpful.

Subsites of the head and neck

The head and neck region is divided into a number of subsites as outlined in **Table 26.2**.

TUMOURS OF THE HEAD AND NECK

Tumour typing

There is a multitude of benign and malignant tumours that affect the head and neck region. Benign and malignant tumours can be classified according to the proposed tumour cell origin (histogenesis) and/or its differentiation pathway (**Table 26.3**). This section is not intended to be an exhaustive account of the pathology of benign and malignant tumours affecting the head and neck region, which can be found in any head and neck pathology text.[10–12] We will cover those benign and malignant tumours that are more commonly encountered in clinical practice, and are exemplars of their type.

BENIGN TUMOURS

Benign epithelial tumours

SQUAMOUS CELL PAPILLOMAS

Squamous cell papillomas are benign epithelial lesions that can affect the oral cavity, larynx, sinonasal tract and nasopharynx. They are typically polypoidal or verrucoid lesions arising from the epithelial surface and can be solitary or multiple lesions depending on site and subtype.

TABLE 26.2 Head and neck cancer sites and subsites

Head and neck site	Subsite
Oral cavity (from lips to anterior tonsil fauces)	• Lips • Anterior tongue • Buccal mucosa • Retromolar trigone • Floor of mouth
Oropharynx (from level of hard palate to hyoid bone)	• Tongue base • Tonsils • Lateral and posterior pharyngeal wall
Hypopharynx	• Pyriform fossa/sinus • Post-cricoid region • Posterior pharyngeal wall
Larynx (from epiglottis to lower border of cricoid cartilage)	• Supraglottis: epiglottis to false cords • Glottis: false cords to 5–10 mm below true cords • Subglottis: 10 mm below true cord to lower border of cricoid cartilage
Nasal cavity and paranasal sinuses	• Nasal cavity • Maxillary sinus • Frontal sinus • Ethmoid sinus • Sphenoid sinus
Nasopharynx	
Ear	• External auditory canal • Middle ear • Inner ear
Salivary gland	• Parotid gland • Submandibular gland • Sublingual gland • Minor glands
Thyroid gland	
Parathyroid glands	
Neck	• Level I, submandibular IB and submental IA nodes • Level II, upper jugular nodes divided by spinal accessory nerve into IIA and IIB • Level III, middle jugular nodes • Level IV, lower jugular nodes • Level V, posterior triangle nodes divided by spinal accessory nerve into VA and VB • Level VI, anterior compartment
Skin	

TABLE 26.3 Classification of tumours

Cell type		Examples	
		Benign	**Malignant**
Epithelial		• Squamous cell papilloma • Pleomorphic adenoma • Warthin's tumour	• Squamous cell carcinoma • Mucoepidermoid carcinoma • Acinic cell carcinoma • Adenocarcinoma • Adenoid cystic carcinoma
Mesenchymal	• Nerve • Vascular • Smooth muscle • Skeletal muscle • Fibrous • Adipose tissue • Bone • Cartilage • Immune system	• Schwannoma, neurofibroma • Angioma • Leiomyoma • Rhabdomyoma • Fibroma • Lipoma • Osteoma • Chondroma	• Malignant peripheral nerve sheath tumour • Angiosarcoma • Leiomyosarcoma • Rhabdomyosarcoma • Fibrosarcoma • Liposarcoma • Osteosarcoma • Chondrosarcoma • Lymphoma
Neuroectodermal			• Malignant melanoma • Olfactory neuroblastoma • Neuroendocrine carcinoma

TABLE 26.4 Pathological features of oral squamous cell papillomas[12]

Subtype	Squamous cell papilloma or verruca vulgaris	Condyloma acuminatum	Multifocal epithelial hyperplasia (Heck's disease)
HPV status	• Approximately half are associated with HPV infection • Squamous cell papilloma HPV6 and 11 • Verruca vulgaris HPV2, 4, 40 and 57	• Associated with HPV6 and 11 • Transmission is venereal or autoinoculation and there is an association with genital condyloma	• HPV13 and 32. • Disease of children, adolescents and young adults
Macroscopic appearance	Wart-like exophytic lesion	Dome-shaped exophytic nodules, which are usually larger than squamous cell papillomas	Multiple clusters or patches of soft, plaque-like lesions

Oral cavity and oropharynx

The pathological features of oral cavity and oropharynx papillomata are outlined in **Table 26.4**.

Larynx

Squamous cell papilloma (and recurrent respiratory papillomatosis) is the most common benign epithelial neoplasm affecting the larynx. It has a bimodal distribution with a peak before the age of 5 and a second between 20 and 40 years of age. There is convincing evidence that recurrent respiratory papillomatosis is due to human papillomavirus (HPV) infection, with HPV6 and 11 as the dominant subtypes.[13] Macroscopically, the lesions are exophytic or sessile with a fine lobular surface that can be prone to bleeding when subjected to even minor trauma. Microscopically, the lesions have a typical papilloma appearance with hyperplastic squamous epithelium covering fibrovascular cores. Branching papillae covered by thin squamous epithelium may be seen, associated with a basal and parabasal cell proliferation. Koilocytes are often focally present in the upper and superficial zones and contain perinuclear halos. IHC and other studies can be used to confirm evidence of HPV infection, but are not required for diagnosis, treatment or to predict clinical behaviour.

Sinonasal tract

Unlike the oral cavity and the larynx, papilloma of the sinonasal tract is relatively uncommon. Sinonasal papillomas arise from the ectodermally-derived ciliated epithelium of the nasal cavity, termed the 'Schneiderian membrane'. There are three morphologically distinct types of papilloma:[14]

- *Exophytic sinonasal papilloma* typically arises on the septum around the nasal vestibule. It closely resembles verruca vulgaris and is associated with HPV6 and HPV11 infection. Malignant transformation is uncommon (**Figure 26.4a**).
- *Inverted sinonasal papilloma* may present anywhere within the nose and paranasal sinuses, occasionally elsewhere within the upper aerodigestive tract (e.g. larynx, lacrimal apparatus). It shows a complex, arborescent exo-endophytic growth pattern with primary, secondary and tertiary ramifications into underlying stroma. Numerous intra-epithelial microabscesses are characteristic and stain for macrophage

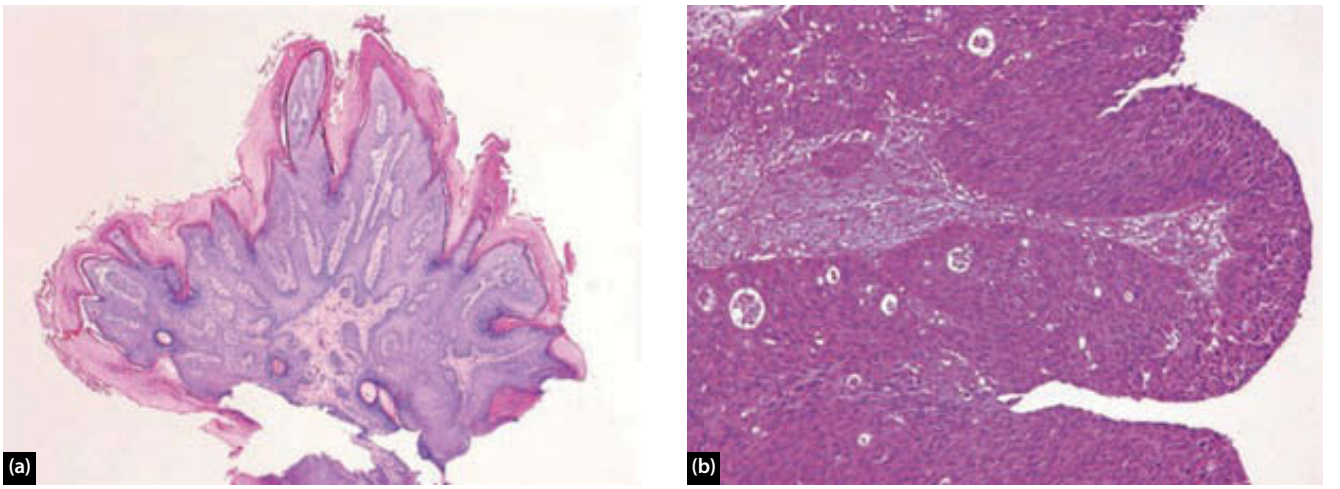


Figure 26.4 Sinonasal papilloma. (a) Exophytic sinonasal papilloma characterized by its radially symmetrical, hyperkeratotic outline (H&E stain, ultralow magnification). **(b)** Inverted sinonasal papilloma illustrating a papillary surface. The tumour is composed of non-keratinizing squamous and transitional epithelium with scattered intra-epithelial microabscesses (H&E stain, medium magnification).

markers (CD68). The epithelium may be squamous (usually non-keratinizing), respiratory, glandular, transitional cell-like or a mixture in any combination or permutation. Varying rates of HPV infection are reported, around a third are considered to be HPV-positive, usually with HPV6 and HPV11. The tumours may be synchronously or metachronously multicentric and because it is difficult to achieve adequate surgical clearance, there is a risk of persistence/recurrence. With each recrudescence, the likelihood of malignant transformation increases (**Figure 26.4b**).

- *Oncocytic sinonasal papilloma* (cylindrical cell papilloma) is not associated with HPV infection. It comprises exophytic fronds of bi-layered, well polarized, oncocytic epithelium supported by a fibrovascular stroma. Microabscesses confined to the epithelium are invariable. There is a predilection for persistence/recurrence if incompletely excised. A small proportion (3–17%) of oncocytic sinonasal papillomas harbour a carcinoma, consequently judicious sampling of the biopsy material is essential.

Benign salivary gland tumours

Benign salivary gland tumours are classified according to WHO and are listed in **Table 26.5**.

PLEOMORPHIC SALIVARY ADENOMA

Pleomorphic salivary adenoma (PSA; benign mixed tumour) is the most common tumour affecting the salivary glands. The annual incidence is reported as 2.4–3.05/100 000. It comprises approximately 50% of all salivary gland tumours, 65% of parotid tumours and 40% of intra-oral minor salivary gland tumours.[15]

Macroscopic appearance

PSA tends to be well demarcated, round or ovoid with broad-based surface bosselations. There may be areas of cystic change and also calcification. They are variably encapsulated and, where present, the capsule may be thick and fibrotic or attenuated and incomplete. The cut surface may either be homogeneous or variegated, dependent upon the precise histological pattern (**Figure 26.5**). Protuberant peri-capsular nodules may be seen, sometimes attached to the main body of the tumour by a slender pedicle. Simple enucleation of the body of a pleomorphic adenoma risks detaching these nodules, which remain behind forming a nidus for recurrence. Predominantly myxoid examples may be semi-fluid and fluctuant – peri-operative capsular rupture and spillage may seed tumour throughout the operative field, increasing the risk of recurrence. Such recurrences are typically multifocal (**Figure 26.6**).

Microscopic appearance

The basic components of a PSA are ductal elements and myoepithelial cells embedded in a chondromyxoid matrix. The appearances vary widely both between PSAs and within the same tumour. A panoply of other changes may be superimposed or even predominate, for example, metaplastic changes (squamous, lipomatous, osseous, neuroid, angiomatoid), degeneration (cystic change, infarction, mineralization, hyalinization, elastosis), specific growth

TABLE 26.5 WHO classification of benign epithelial salivary gland tumours[12]

Benign epithelial salivary gland tumours
• Pleomorphic adenoma • Myoepithelioma • Basal cell adenoma • Warthin's tumour • Oncocytoma • Lymphadenoma • Cystadenoma • Sialadenoma papilliferum • Ductal papillomas • Sebaceous adenoma • Canalicular adenoma

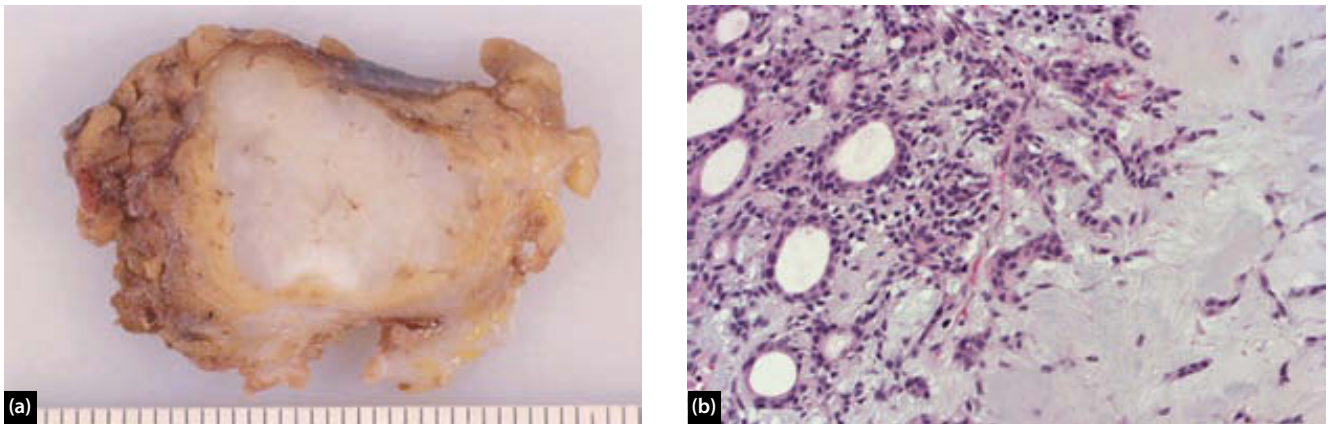


Figure 26.5 Pleomorphic salivary adenoma. **(a)** Cut surface of the tumour displaying a solid blue/grey hue characteristic of chondromyxoid matrix. **(b)** Histology showing double layered ducts and strands of myoepithelial cells invested by a myxoid matrix (H&E stain, medium magnification).

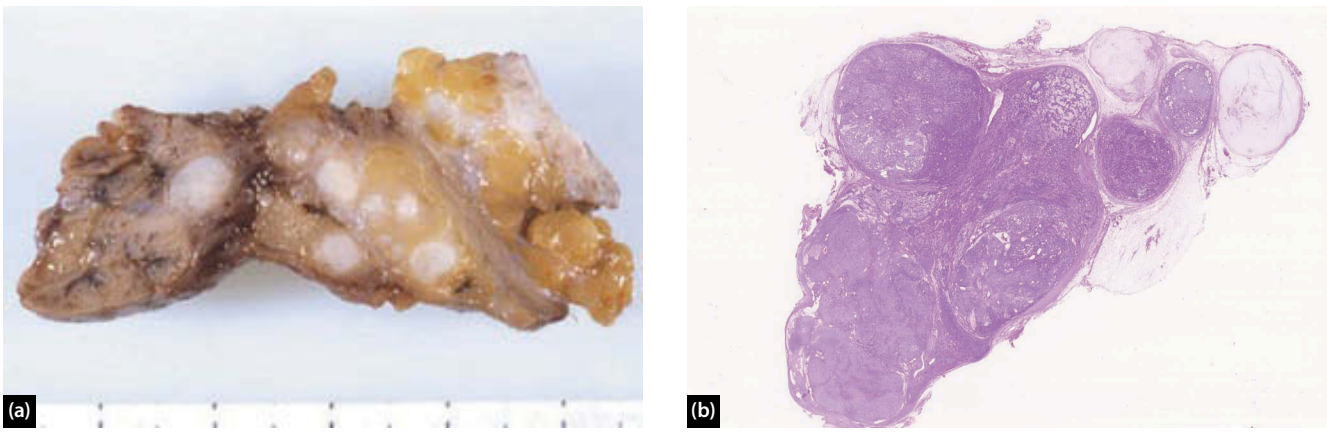


Figure 26.6 Recurrent pleomorphic salivary adenoma. **(a)** Excision of multi-focal recurrence of pleomorphic salivary adenoma encompassing the original surgical field. **(b)** Whole mount section of another local recurrence showing secondary seeding of fat, residual salivary gland and fibrous tissue. The nodules are clearly of differing composition despite having arisen from the same parent lesion [H&E stain, ultralow magnification].

patterns (e.g. adenoid cystic carcinoma-like, clear cell, epithelial-myoepithelial carcinoma-like, basaloid, giant cell, spindle cell, acinar, plasmacytoid, oncocytoid) and crystal deposition. This heterogeneity can occasionally make diagnosis difficult, especially from limited samples derived from FNAB or core biopsies.

Risk of malignant transformation

PSA has a risk of malignant change, around 6%. Clinical features that are associated with an malignant transformation include:[12, 15, 16]

- older patient age
- male patient
- long duration of tumour
- multiple recurrences
- deep lobe parotid location.

WARTHIN'S TUMOUR

Warthin's tumour (adenolymphoma, papillary cystadenoma lymphomatosum) is the second most common tumour of the salivary glands.[17] It is exclusive to the parotid gland and para-parotid lymph nodes and can be multicentric and/or bilateral in 4–10% of cases. It comprises between 3.5% and 30% of primary epithelial salivary gland tumours with geographical variation. It occurs in Caucasians and Asians with a lower incidence in African-Americans and Black Africans. It can occur over a wide age range, but is common in the sixth decade for women and seventh decade for men. It is more common in males but the male:female ratio has reduced over the last few decades. There is a link between Warthin's tumour and cigarette smoking.[18]

Macroscopic appearance

The tumour is a circumscribed, often thinly encapsulated soft mass that contains multiple cystic and solid/papillary areas, which is white to brown in colour. There may be coagulated tan exudate in the cystic spaces (**Figure 26.7a**).

Microscopic appearance

Warthin's tumour is composed of ciliated, bi-layered oncocytic epithelium supported by reactive lymphoid

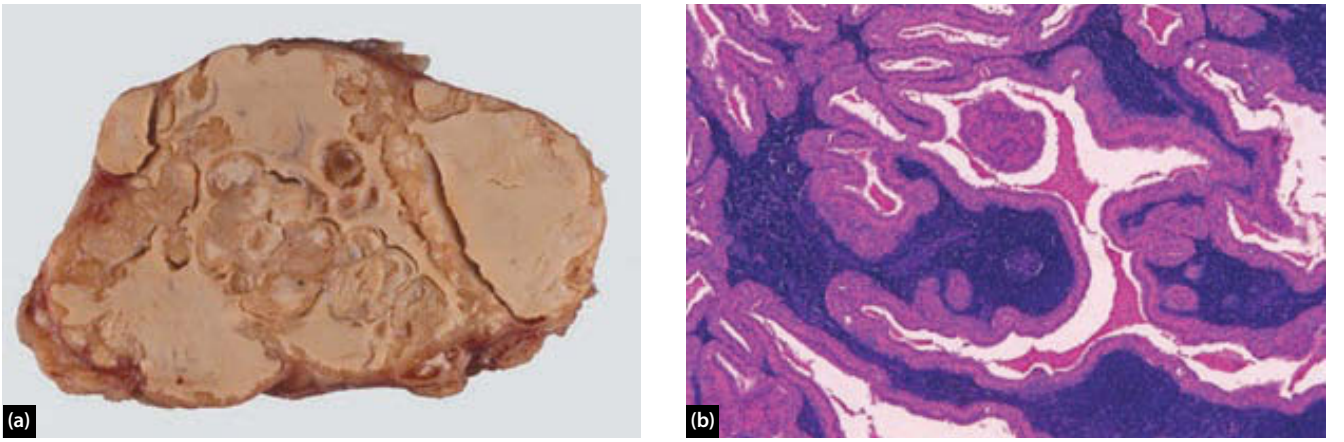


Figure 26.7 Warthin's tumour. (a) The characteristic papillary-cystic cut surface appearance of Warthin's tumour. Oncocytic epithelium is typically mid-brown. The light tan micronodules correspond to reactive lymphoid follicles. **(b)** Papillary-cystic tumour composed of fronds of oncocytic epithelium supported by hyperplastic lymphoid stroma (H&E stain, low magnification).

stroma (**Figure 26.7b**). The cystic areas contain amorphous debris. Warthin's tumour can undergo infarction or degeneration and metaplastic change either spontaneously or secondary to manipulation (e.g. FNAB, core biopsy). Benign oncocytic epithelial inclusions are commonly seen in intraparotid and para-parotid lymph nodes. These inclusions probably account for Warthin's tumour's propensity for multicentricity and bilaterality. Malignant transformation, either carcinomatous or lymphomatous, is rare.

Benign mesenchymal tumours

SCHWANNOMA

Schwannomas (neurilemmomas) are benign encapsulated tumours that originate from the Schwann cells of the peripheral nerve sheath. Schwannoma in the head and neck may arise from the cranial nerves including Vth and VIIth–XIIth, sympathetic chain, cervical or brachial plexus. It is the most common neoplasm affecting the temporal bone, vestibular Schwannoma, and a common site of occurrence is the neck, but it is rare in the oral cavity.[19] The NF2 gene is inactivated in 67% of Schwannomas.[20,21] Approximately 2% are due to neurofibromatosis 2, which is an uncommon autosomal dominant condition characterized by the presence of bilateral vestibular Schwannomas and an increased incidence of extra- and intracranial meningiomas.

Macroscopic appearance

Schwannomas are typically encapsulated, but those affecting the temporal bone tend to be non-encapsulated (**Figure 26.8**). The tumour is usually attached to an identifiable nerve and is firm and rubbery with a tan-white to yellow colour. At operation, it may be mistaken for a lymph node and excised without seeking to preserve or repair the nerve, thereby sustaining unexpected neurological damage.

Microscopic appearance

The tumour consists of a mixture of Antoni A and Antoni B areas. Antoni A areas are formed by short fascicles of closely packed monomorphous spindle cells with fibrillar cytoplasm. The cells sometimes form a palisaded arrangement around acellular, collagenized foci known as Verocay bodies. Antoni B areas are composed of the spindle cells haphazardly arranged within a loose myxoid stroma. Secondary areas of vascular wall hyalinization, microcystic degeneration, haemorrhage, foam cell infiltration and calcification may be seen. Focal bizarre, hyperchromatic and multinucleate giant cell transformation is sometimes encountered. In the absence of increased numbers of mitoses, abnormal mitotic spindles, necrosis or other atypical features, this is designated ancient change, probably a degenerative phenomenon, which is of no known clinical relevance. On IHC, Schwannomas are strongly S100-positive; neurofibromas tend to be weakly positive and also contain neurofilament positive fibres. However, occasionally distinction between Schwannoma and neurofibroma is problematic, invoking the rubric 'benign peripheral nerve sheath tumour'.

MALIGNANT TUMOURS

Malignant disease of the head and neck is the sixth most common form of cancer worldwide with around 300 000 new cases per annum. In the UK there were 11 449 cases of head and neck cancer in 2014 and 3225 deaths, equating to an incidence of 25 per 100 000 (7918 cases) in males and 11 per 100 000 (3531 cases) in females.[22] The majority (90%) of head and neck malignancies are squamous cell carcinomas arising from the epithelial-lining of the upper aero-digestive tract.

Tumour staging

Cancer of the head and neck, due to the diversity of pathology and the variation in progression at different anatomical subsites, cannot be meaningfully staged by a single, generic schema. The tumour, node, metastasis (TNM) staging system, developed and maintained by both the American Joint Committee for Cancer (AJCC) and the International Union Against Cancer (UICC), is the most

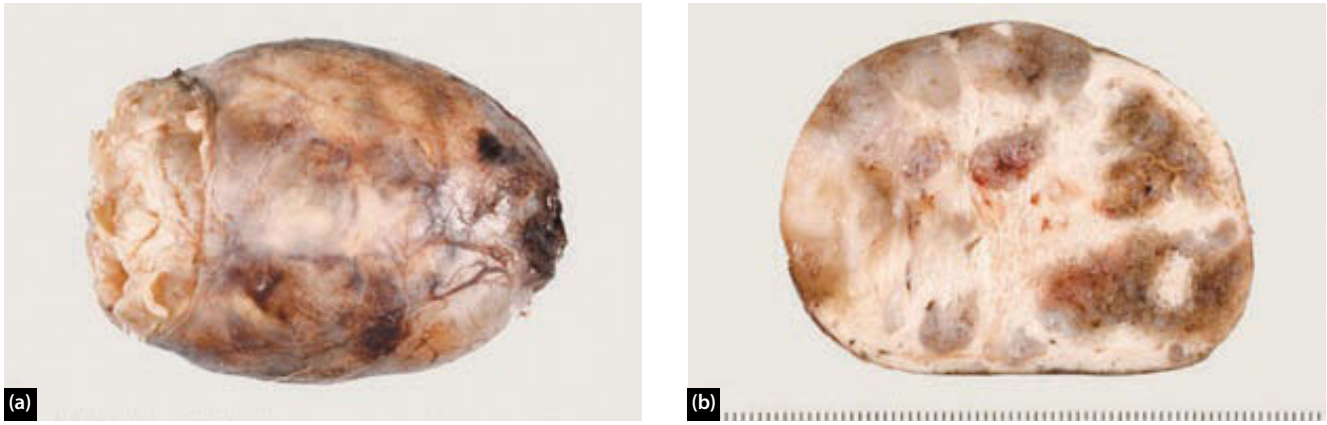


Figure 26.8 Schwannoma. **(a)** Encapsulated Schwannoma from the parapharyngeal space giving a smooth surfaced nodal appearance, although the capsule is deficient at one pole. **(b)** The cut surface displays a variegated texture.

widely used method for staging.[23, 24] There are international expert committees that keep the system under review and the 8th edition was published by both the AJCC and UICC in 2017.[24] There have been major changes in TNM staging of the head and neck cancer, when compared to the 7th edition published in 2010,[23] and it remains to be seen how widely this will be adopted and implemented by the head and neck oncology community.

The basic principles of the TNM staging system are:

- *Clinical*. cTNM or TNM is based on clinical findings (physical examination and imaging) and assigned prior to starting first definitive treatment.
- *Pathological*. pTNM is based on the cTNM modified by further information obtained from surgery and subsequent pathological examination.
- *Autopsy*. aTNM is used when the cancer is only classified from the results of post-mortem examination and no evidence of cancer was evident prior to death.

Other descriptors of TNM may occasionally be used and include:

- the 'm' suffix, which is used when there is more than one primary at a single site, pT(m)NM
- the 'y' prefix, which is used when classification is performed during or after initial multimodality therapy, ycTNM or ypTNM.

Tumour differentiation refers to how well developed or mature the malignant cells are. Well-differentiated cells resemble normal cells and tend to grow and spread at a slower rate. There is often morphological heterogeneity, however, both between different tumours of the same type and within the same tumour. Conventionally, tumours are histologically subtyped according to their differentiated components. They are graded with reference to their worst differentiated elements on the premise that it is these that will behave most aggressively, and thereby be the major determinant of prognosis:

- Gx – grade cannot be assessed
- G1 – well-differentiated
- G2 – moderately differentiated
- G3 – poorly differentiated.

The presence or absence of residual tumour is classified as:

- Rx – the presence of residual tumour cannot be assessed
- R0 – no residual tumour is present
- R1 – microscopic residual disease
- R2 – macroscopic residual tumour.

The UICC or AJCC TNM atlas provides detailed descriptions of T-, N- and M-categories for each anatomical sub-site. TNM provides an indication of the amount and spread of the disease. The TNM categories are then used to assign a stage grouping, which relates to prognosis.[23, 24]

Carcinomas

SQUAMOUS CELL CARCINOMA

Squamous cell carcinoma (SCC) and its variants represent by far the most common malignant tumour affecting the head and neck region, accounting for approximately 95% of all primary tumours of the oral cavity, oropharynx, hypopharynx, larynx and sinonasal tract. By contrast, SCC is uncommon in the major salivary glands and thyroid, although these may be affected by direct contiguous invasion from neighbouring structures or metastatic spread. Head and neck squamous cell carcinoma (HNSCC) may also arise from skin. Typically, HNSCC spreads by direct invasion or via regional lymphatics, although haematogenous spread, especially to the lungs, is possible.

Squamous epithelial dysplasia

SCC of the oral cavity and larynx is well known to arise from epithelial precursor lesions, which may be localized or represent wider areas of 'field cancerization'. The precursor lesions harbour varying degrees of epithelial dysplasia, defined by the accumulation of architectural and cytological abnormalities. By convention, epithelial dysplasia is graded and numerous systems have been suggested.

The most recent WHO classification recommends that laryngeal dysplasias are assigned low and high grade categories, whereas oral dysplasia are assigned mild, moderate and severe dysplasia (though there is an option to use a high and low grade categories as well).[12] Grading is known to be subjective and prone to inter-observer variation; nevertheless it is still used to guide management. The more severe the dysplasia, the greater the risk of transformation into malignant disease. A meta-analysis of oral dysplastic lesions indicates a malignant transformation rate of 12% and a mean time to transformation of 4.3 years.[25] Similar transformation rates are quoted for laryngeal precursor lesions.[12] It is clear from these data that progression to invasive malignancy is not inevitable, which implies that such lesions may remain stable over time or possess the capacity to regress – indeed most lesions do not proceed to invasive carcinoma within the time period of the studies conducted. Clinically, these lesions are irregular, circumscribed lesions with a white (leukoplakia), red (erthyroplakia) or variegated appearance (erythroleukoplakia). In reality, dysplasia is a dynamic process manifest as a continuous morphological spectrum. Therefore, the rigorous application of discrete categories, whatever their arbitrary histological basis, is destined to be problematical. IHC, molecular and other biomarkers are presently of limited assistance in resolving this issue.

Aetiology

The main risk factors for HNSCC are tobacco and alcohol abuse, which either alone or combined, are implicated in 75% of all HNSCC.[26] Tobacco alone increases the risk of cancer occurrence two- to three-fold, but acts synergistically with alcohol leading to a multiplicative rather than additive increase. Increased duration of exposure to tobacco and/or alcohol increases the risk of developing HNSCC. Tobacco contains a number of known carcinogens (e.g. polynuclear aromatic hydrocarbons), which cause DNA damage leading to gene mutations. Alcohol causes DNA damage and gene mutation by a number of mechanisms. These include the effect of acting as a solvent for other carcinogens, nutritional deficiencies, acetaldehyde (a by-product of alcohol metabolism) and the direct effect of ethanol. Increasingly, it is recognized that HPV, especially HPV16, is an important cause of oropharyngeal SCC.[27] HPV-positive tumours typically affect non-smokers, non-drinkers and younger patients. Patients with HPV-related oropharyngeal SCC have a better overall survival than those with HPV-negative disease.[28] HPV infection at other subsites is less frequent (< 5%) and consequently the data around survival are less convincing. SCC of the lip is associated with sun exposure and pipe smoking. Sinonasal SCC is linked to nickel and chromate exposure and woodworking. Dietary deficiencies have also been linked to the development of HNSCC, especially vitamins (A, C and E), foods (fruit, vegetables and dairy) and elements (e.g. iron especially when associated with iron-deficiency anaemia of Plummer–Vinson (Paterson–Brown–Kelly) syndrome, which is associated with hypopharyngeal SCC). Oral cavity SCC is particularly common in India where a third of all cancers originate in the head and neck. The widespread chewing of betel nut and paan, which causes both oral submucous fibrosis, a recognized oral potentially malignant disorder, and oral cavity SCC has been implicated. HNSCCs are typically sporadic, but a familial inheritance has been noted in some cases. The risk of HNSCC is also increased in patients with any syndrome associated with an increased risk of cancer. Patients with Fanconi's anaemia have a 700-fold increased risk and the cancer is usually diagnosed in the third decade.

Pathogenesis

HNSCC is a heterogeneous disease, but a hypothetical progression model has been proposed.[26] Histological progression from normal epithelium to hyperplasia, dysplasia and finally invasive carcinoma is related to a number of factors, including genetic changes causing genetic instability leading to cellular change.[29] Genetic changes include the sequential inactivation of tumour suppressor genes and activation of proto-oncogenes. Carcinogens produced by tobacco, which include nitrosamines and benz-(a)-pyrene, produce mutations in p53 associated with HNSCC. The molecular changes are due to a number of genetic alterations, which include loss of heterozygosity (LOH) of 9p21, seen in 70–80% of HNSCC. Other abnormalities include LOH 3p, 17p, 11q and 13q. In HPV16 infection the E6 and E7 viral oncoproteins cause inactivation of tumour suppressor molecules, pRb and p53. Loss of pRb causes uncontrolled cell proliferation. Loss of p53-mediated response to DNA damage leads to genomic stability. There is also reactivation of telomerase driving cell immortality.[27, 29]

Macroscopic appearance

HNSCC appearance varies depending on subsite, but can be an exophytic or ulcerative lesion. On the skin, it typically looks like a non-healing scab or ulcer, which can intermittently bleed. On mucosal surfaces, lesions typically start as whitish or reddish plaque-like lesions (leukoplakia or erthyroplakia), which then progress to ulcerated or fungating masses with irregular indurated borders (**Figure 26.9**).

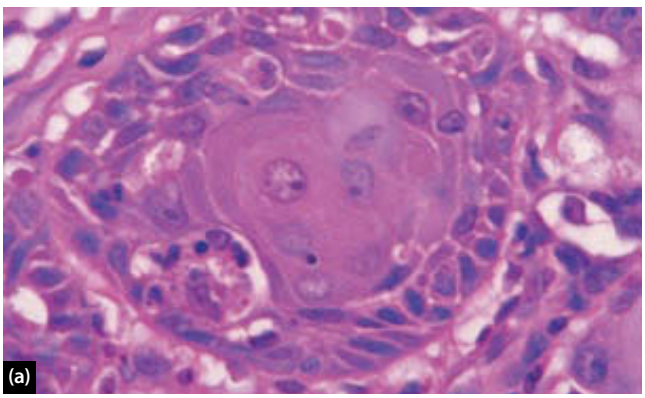
Microscopic appearance

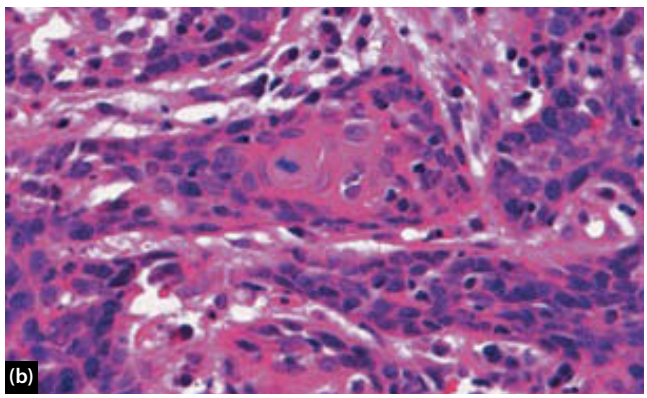
The histological appearance of SCC is very similar across all sites in the head and neck. Well-differentiated and moderately differentiated SCC characteristically shows evidence of keratinization and intercellular prickles (desmosomes) (**Figure 26.10a**). Poorly differentiated SCC lacks evidence of keratinisation and immunohistochemical analysis may be required to support the diagnosis (**Figure 26.10b**).

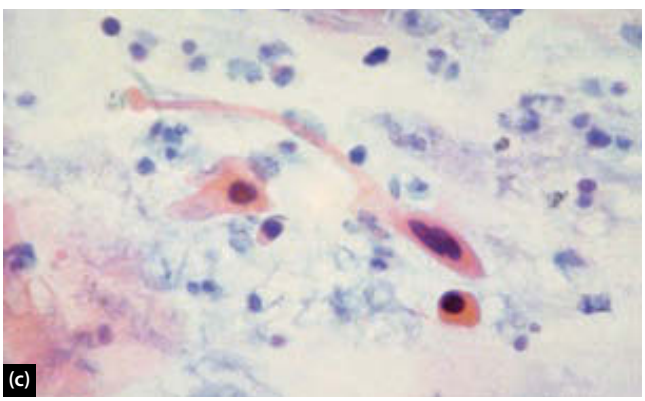
Malignant squamous cells display some or all of the following features:

- irregular shape and orientation
- increased and abnormal mitoses

Figure 26.9 Laryngeal squamous cell carcinoma. **(a)** Total laryngectomy specimen opened in the posterior sagittal plane to show advanced, fungating carcinoma effacing much of the supraglottic larynx with local extension on to the left true vocal cord. **(b)** Transverse section through the specimen confirms bilateral midline tumour herniating through the anterior commissural ligament into anterior strap musculature.







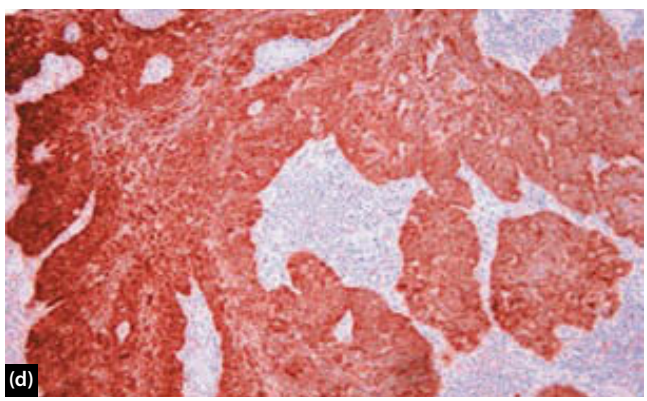


Figure 26.10 Squamous cell carcinoma. **(a)** Moderately differentiated SCC illustrating a focus of keratinization. Note the disordered cell polarity, nuclear pleomorphism (variation in size, shape and intensity of nuclear staining), coarse chromatin and prominent nucleoli (H&E stain, high magnification). **(b)** Poorly differentiated SCC lacking keratinization (H&E stain, medium magnification). **(c)** Cytology preparation from an SCC showing several atypical squamous cells amidst a necrolytic background. Note the large, binucleate caudate ('tadpole') cell, intermediate-sized obovate ('comet') cell and the smaller hyperkeratinizing orangeophilic ('carrot') cell. Other forms commonly seen include fibre ('snake') cells, acanthocytes ('spider') cells and bizarre giant ('monster') cells. Anucleate squames, dissociated keratotic debris, parakeratotic scale ('sprigs') and keratin whorls ('pearls') may accompany these (Pap stain, high magnification). **(d)** Immunohistochemistry showing strong and diffuse nuclear and cytoplasmic p16 expression in an HPV-associated SCC (p16 IHC, medium magnification).

- nuclear hyperchromatism
- coarse and clumped chromatin
- nuclear pleomorphism
- increased nucleus–cytoplasmic ratio
- prominent nucleoli
- premature keratinization (dyskeratosis)
- loss of keratin production
- disordered cell polarity
- disorganized growth.

Cytologically, SCC may be so well differentiated that it is impossible to reliably discriminate it from non-neoplastic squamous epithelium; for example, an FNAB from an inflamed branchial cyst may mimic a cystic metastasis and vice versa. Obviously, the context is all-important and, in experienced hands, FNAB from a cervical lymph node containing abnormal squamous cells against a background of proven SCC may be reasonably taken as presumptive evidence of a secondary deposit until otherwise proven (**Figure 26.10c**). For these reasons, only under exceptional circumstances should radical cancer treatment be undertaken on the basis of a primary diagnosis reached by FNAB without more definitive tissue diagnosis and even then rigorous clinico-radiological correlation must be exercised.

The defining feature of SCC is breach of the subepithelial basement membrane allowing malignant cells to infiltrate into the normal underlying connective tissue, thereby gaining access to lymphatics, blood vessels and nerves. Typically, areas of dysplasia will surround invasive SCC, although this is by no means invariable. The phenomenon of 'field cancerization' reflects the long-term exposure of head and neck mucosa to carcinogens causing genetic alterations, which enable multifocal tumours to arise due to independent genetic events.[29]

The microscopic description of an SCC includes:

- histological subtype
- histological grade (well-, moderate-, poorly-differentiated)
- invasive front (cohesive or non-cohesive)
- vascular invasion
- neural invasion.

The terms 'superficial invasion', 'minimally invasive carcinoma' and 'micro-invasive carcinoma' are sometimes used to denote SCC with limited infiltration. However, these presently have no agreed, validated definition and are, therefore, potentially confusing. It is more helpful to measure tumour depth and/or thickness and overall dimensions, and place this within the recognized TNM schema with any relevant subjective descriptive comments. It is also important to assess for the presence of malignant cells within lymphovascular channels and also neurotropism, signifying vascular or neural invasion respectively, both of which are associated with an unfavourable prognosis.

Immunohistochemistry

For poorly differentiated tumours, IHC is required to render an accurate diagnosis. The initial panel of IHC is directed at identifying broad groups of tumours: carcinoma, melanoma, lymphoma and sarcoma. A pan-cytokeratin cocktail is used to demonstrate cytokeratin intermediate filaments, which is positive in virtually all carcinomas. S100, MelanA, HMB45 and Sox10 can be used to identify melanoma. CD45 (leucocyte common antigen), CD79a (B cell marker) and CD3 (T cell marker) are used to identify lymphoma. Sarcomas are more variable and panels are formulated based on morphological clues. Antibodies for desmin and vimentin are often used to start the process of investigation.

For poorly differentiated carcinomas, cytokeratins 5, 6, 14, and staining with the nuclear proteins p40 and p63, are used to support a diagnosis of poorly differentiated SCC. The results of these panels of IHC are usually described in the pathology report.

For oropharyngeal SCC, HPV testing is recommended.[30] Tests are carried out for prognostication and for entry into clinical trials. Typically, testing is carried out using a combination of p16 IHC and high-risk HPV DNA ISH (**Figure 26.10d**).[31] Other HPV specific tests, such as polymerase chain reaction (PCR)-based tests have also been validated. Tumours that harbour oncogenic HPV show increased p16 expression. There is strong and diffuse, nuclear and cytoplasmic staining in more than 70% of malignant cells. p16 is a recognized surrogate marker of oncogenic HPV infection; the test is highly sensitive but lacks specificity. By contrast, high-risk HPV DNA ISH is highly specific but lacks sensitivity. The combination of both tests provides a satisfactory classification for the majority of oropharyngeal SCC (95%). The significance of p16-positive, HPV-negative SCC is controversial; in some studies p16 is an independent marker of good prognosis, whereas in other studies p16 positivity alone does not confer a favourable prognosis.[32, 33]

For the clinical scenario of an enlarged cervical lymph node that turns out to be metastatic SCC, HPV and EBV tests (see below) are useful in locating the putative primary site. HPV-positive SCCs are usually located in the oropharynx, whereas EBV-positive SCCs are typically discovered in the nasopharynx. A similar strategy can be used to link a distant metastases to an index primary tumour in the head and neck region.

HNSCC variants

A number of morphological variants of SCC are recognized, which include: verrucous carcinoma (VC); spindle cell carcinoma (sarcomatoid carcinoma); papillary SCC; adenosquamous carcinoma; and basaloid SCC.

- VC is a controversial manifestation of well-differentiated SCC, typically occurring in the oral cavity but rarely said to occur in the larynx (1–3% of all laryngeal malignancies), hypopharynx, sinonasal tract and nasopharynx, plus other sites outside the head and neck. Clinically, VC is a warty, exophytic lesion that arises from a broad base. It has a superficial spreading growth, but can be deeply destructive extending

into muscle, cartilage or bone. Histologically, VC lacks significant cellular atypia and is characterized by blunt incursions and an expansile advancing margin sometimes eliciting brisk lymphocytic response. If adequately sampled, approximately 20% of VCs contain areas of conventional SCC, although often very localized, and it is these elements that determine overall prognosis. Incision biopsy diagnosis of VC is problematic as its predominant bland morphology may be indistinguishable from benign squamoproliferative lesions on superficial or limited volume material. Typically, three or four biopsies are required, or even excision biopsy, before the overall architecture is appreciated and the diagnosis is seriously considered. A high index of pathological suspicion and clinical persistence are thus prerequisites.

- Spindle cell carcinoma (sarcomatoid carcinoma) (**Figure 26.11**) occurs in the upper respiratory tract or, less commonly, in the oral cavity. Patients are typically elderly males and a significant number will have had previous radiation. Spindle cell carcinoma usually has a polypoidal, exophytic configuration with either a broad base or narrow pedicle that can occasionally auto-amputate and be expectorated by the patient. The surface tends to be ulcerated. It is usually a bi-phasic lesion with areas of SCC, and/or high-grade dysplasia, associated with bizarre spindle cell and/or giant cell proliferation of sarcomatoid appearance. The squamous component can be difficult to identify due to the ulceration and the sarcoma-like component predominates. IHC may be helpful, although the spindle cells are often negative for epithelial markers and a significant minority paradoxically co-express aberrant positivity for mesenchymal markers.
- Papillary SCC is an uncommon variant.[34] It may affect most anatomical subsites of the head and neck, including the larynx and hypopharynx. Macroscopically, the tumour is similar to VC, but lacks the typical surface keratinization. Microscopically, the lesion is composed of obviously atypical squamous cells overlying fibrovascular papillary stromal cores. The tumour behaves in a similar manner to conventional SCC and management is therefore similar.
- Adenosquamous carcinoma is an uncommon variant of HNSCC, which is considered aggressive and associated with a poor prognosis.[35] It predominantly affects males in the sixth or seventh decade. The larynx, and occasionally the hypopharynx, is the most commonly affected site. Macroscopically, the tumour resembles a typical HNSCC. Microscopically, the tumour is characterized by the presence of conventional SCC admixed with a variable proportion of true glanduloductal elements indicative of divergent differentiation. Mucin histochemistry and keratin immunoprofiling may aid distinction from acantholytic SCC with pseudoglandular growth and also from mucoepidermoid carcinoma.
- Basaloid SCC is a high-grade aggressive variant of SCC typically found in middle-aged male patients, affecting the oropharynx, larynx and hypopharynx.[36] Macroscopically, these are firm to hard tumours with central necrosis and superficial ulceration. Microscopically, the tumour is infiltrating and deeply invasive and presents a typical basaloid appearance consisting of pleomorphic cells arranged in a lobular configuration with palisading. Cystic degeneration with central comedonecrosis is often a feature. There may be minimal objective evidence of squamous cell differentiation.

Other variants include acantholytic, small cell, clear cell, giant cell and lymphoepithelial carcinoma. In practice, many SCCs are heterogeneous in pattern at least focally.

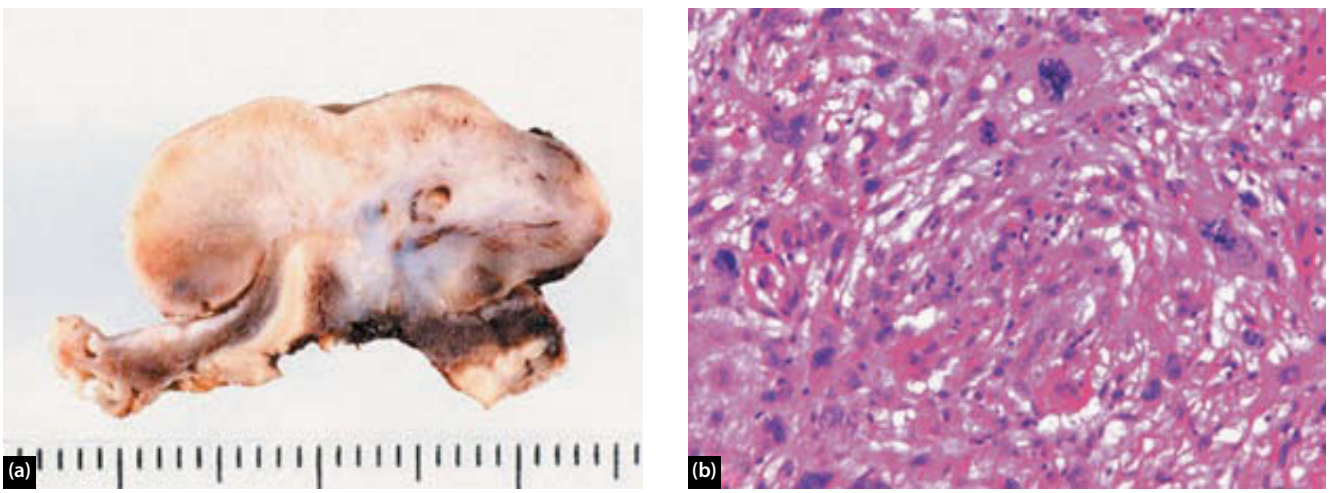


Figure 26.11 Spindle cell carcinoma of larynx. (a) Cross-section of epiglottic resection specimen. This is ulcerated and polypoidal, but also infiltrates deeper, penetrating into and through epiglottic cartilage. **(b)** Representative field beneath the tumour surface exhibiting highly pleomorphic spindle and bizarre giant cells with abnormal mitoses reminiscent of undifferentiated pleomorphic sarcoma (H&E stain, high magnification).

NASOPHARYNGEAL CARCINOMA

Nasopharyngeal carcinoma (NPC) is a distinct type of SCC arising in the nasopharynx.[37] Worldwide, NPC is an uncommon disease with an incidence of less than 1 per 100 000, but has a very distinct geographical distribution. In China, 18% of all adult cancers are NPC and it is especially common in northern provinces, Kwantung and Taiwan, but is uncommon in children (2%). By contrast, 10–20% of all paediatric cancers in northern and central Africa are NPC. Ethnic groups with intermediate risk include Greenland Inuit and the Maghrebis of Northwest Africa, but Caucasian populations have the lowest risk. Other factors implicated in the development of NPC include EBV and dietary factors, especially a high intake of salted fish and preserved vegetable products. Clinically, the tumour can be a bulging, exophytic and lobulated, or ulcerative mass. Occasionally, there may be no visible tumour, necessitating blind biopsy of the nasopharynx.

Microscopically, NPC is classified according to the WHO system, which is dependent on the presence or absence of keratinization. Around a quarter of tumours contain more than one type and are then classified according to the dominant type:

- Keratinizing NPC represents approximately 25% of all NPC in North America, but only 2% of Chinese patients.[37] This type is rarely found in patients under 40 years of age. Like HNSCC in other sites, this type of NPC can be classified as well, moderately or poorly differentiated. The cells grow in well-defined nests with easily demonstrable intercellular bridges and keratin pearl formation. The stroma undergoes a desmoplastic response to invasive growth.
- Non-keratinizing NPC, which is associated with EBV, can be divided into differentiated or undifferentiated, but is of no clinical or prognostic significance:
  - Differentiated non-keratinizing NPC is the least common subtype, accounting for 12% worldwide (2% in China).[37] As the name suggests, there is little or no evidence of keratinization, vague intercellular bridges and it may undergo cyst formation. There is no desmoplastic response to invasive growth.
  - Undifferentiated non-keratinizing NPC is the most common subtype, accounting for approximately 63% of cases, rising to 95% in China,[37] and is the most common type to affect children. The cells possess round nuclei, prominent eosinophilic nucleoli, and/or dispersed or microvacuolated chromatin with scant cytoplasm. There is generally a prominent non-neoplastic intra-tumoral and peri-tumoral lymphoid cell infiltrate. When there is a diffuse, non-cohesive growth pattern, such malignant cells are easily overlooked on cursory inspection. Other recognized growth patterns include cohesive or nested cells. There is no desmoplastic response to invasive growth.

EBV infection can be reliably detected in biopsy specimens using ISH for EBV encoded early RNA (EBER) (**Figure 26.12**). The majority (90%) of Asian NPCs are EBV-positive. There is emerging evidence that some of NPCs are HPV-positive, typically those that occur in Caucasian patients.[38]

MALIGNANT SALIVARY GLAND TUMOURS

Malignant salivary gland tumours are very uncommon and represent approximately 0.5% of all malignancies,

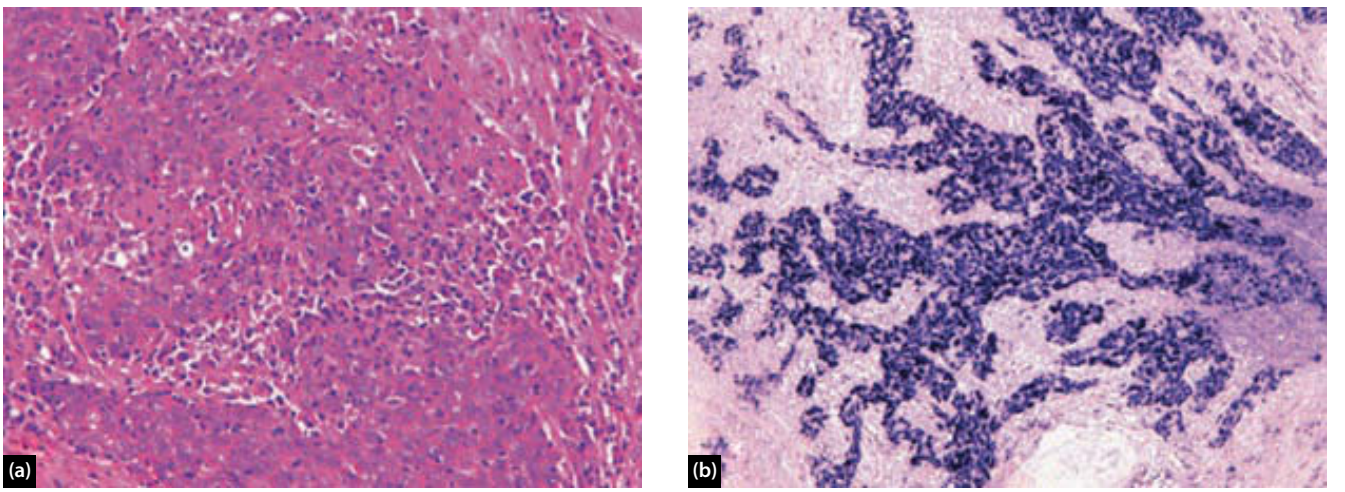


Figure 26.12 Epstein–Barr virus (EBV)-associated undifferentiated carcinoma of nasopharyngeal type. (a) Sheets of poorly differentiated, non-keratinizing malignant cells with ill-defined cytoplasmic borders imparting a syncitial appearance. The nuclei are variously vacuolated or nucleolated. Small lymphocytes are present within and surrounding the tumour cells (H&E stain, medium magnification). **(b)** *In situ* hybridization (ISH) for EBER confirms a diffusely positive signal indicating EBV infection (EBER ISH, medium magnification).

TABLE 26.6 WHO classification of malignant epithelial salivary gland tumours[12]

Malignant epithelial salivary gland tumours
• Mucoepidermoid carcinoma
• Acinic cell carcinoma
• Adenoid cystic carcinoma
• Adenocarcinoma NOS
• Carcinoma ex-pleomorphic adenoma
• Polymorphous adenocarcinoma
• Clear cell carcinoma
• Basal cell adenocarcinoma
• Intraductal carcinoma
• Salivary duct carcinoma
• Myoepithelial carcinoma
• Epithelial/myoepithelial carcinoma
• Secretory carcinoma
• Sebaceous adenocarcinoma
• Carcinosarcoma
• Poorly differentiated carcinoma
• Undifferentiated carcinoma
• Small cell neuroendocrine carcinoma
• Large cell neuroendocrine carcinoma
• Lymphoepithelial carcinoma
• Squamous cell carcinoma
• Oncocytic carcinoma
• Sialoblastoma

5% of all head and neck cancers and an incidence in the Western world of 2.5–3/100 000/year.[13] Despite the low incidence, over 20 named malignant salivary gland neoplasms are recognized (**Table 26.6**). This section will describe the pathological characteristics of the more common malignant neoplasms and the authors recommend reference to a specific head and neck pathology atlas for information regarding less common tumours.[11, 12]

MUCOEPIDERMOID CARCINOMA

Mucoepidermoid carcinoma typically affects the parotid gland, but may also occur in the minor salivary glands. The tumour is triphasic comprising goblet cell mucocytes, epidermoid cells (usually with no keratinization) and non-descript cells of intermediate size and shape.

Epidemiology

Mucoepidermoid carcinoma is the most common malignant salivary gland neoplasm (12–29% of all salivary gland malignancies).[11, 12] It is found more frequently in female patients and can present at any time between the first and ninth decade, but peaks in the fifth decade. The major risk factor for development is previous therapeutic radiation exposure with a latent period of 7–32 years.[11, 12]

Macroscopic appearance

The tumour has a variety of appearances. It can be circumscribed or infiltrative. Tumours are predominantly solid, tan-white to pink masses, often cystic filled with a viscous brown fluid. Areas of scarring can also be present and may occasionally prevail.

Microscopic appearance

The tumour consists of varying proportions of admixed mucinous, epidermoid and intermediate cells (**Figure 26.13**). Low-grade tumours are macrocystic and microcystic with plentiful mucocytes, fewer epidermoid cells and infrequent intermediate cells. Extravasated, dissecting mucin pools may be seen. There may be a sclerosing/fibrosing component. Reactive tumour-associated lymphoproliferation is characteristic. High-grade tumours are more solid and contain fewer mucinous elements with a preponderance of atypical epidermoid cells. High-grade tumours are easily mistaken for SCC and recourse to exhaustive sampling augmented by a panel of mucin histochemistry may be diagnostic. This diversity makes FNAB interpretation challenging. The behaviour of mucoepidermoid carcinoma is very varied and various systems have been proposed to attempt to grade tumours and hence predict outcome. A commonly used system is outlined in **Table 26.7**.[39]

ACINIC CELL CARCINOMA

Epidemiology

Acinic cell carcinoma accounts for 7–17.5% of all malignant salivary gland neoplasms. Approximately 80% arise from the parotid gland, with the remaining 20% arising mainly from the minor salivary glands or submandibular glands, and only 1% from the sublingual gland. There is a male preponderance and they usually present in the third decade of life.[11, 12]

Macroscopic appearance

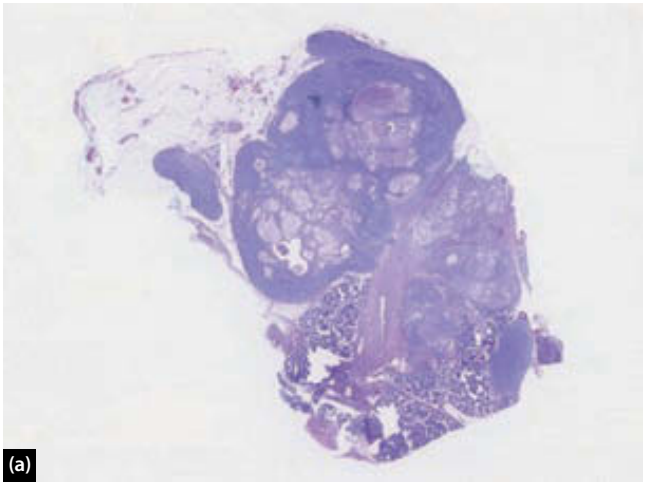
Macroscopically, the tumours are of a firm to rubbery consistency and range in colour from a tan-grey to yellow or pink mass. They are usually rounded, well circumscribed and can be encapsulated. They can contain areas of haemorrhage or cystic change. Recurrent tumours tend to be less well demarcated and can appear multinodular.

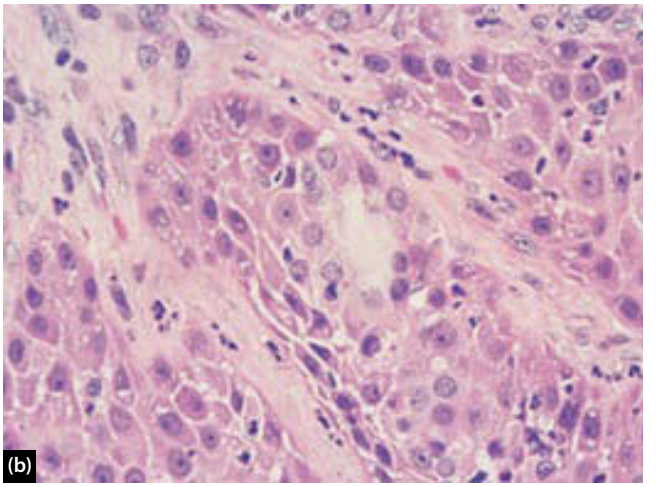
Microscopic appearance

Acinic cell carcinomas recapitulate the serous acinar cell of normal salivary gland tissue. There are a number of recognized growth patterns, which can coexist in a single tumour (**Table 26.8**). Histochemical stains are used to demonstrate zymogen granules in serous acinar cells; in some tumours these cells are sparse, making diagnosis challenging (**Figure 26.14**). Reactive lymphoid tissue is characteristic of acinic cell carcinoma and may mimic lymph node involvement.[40]

ADENOCARCINOMA NOT OTHERWISE SPECIFIC

Adenocarcinoma not otherwise specified (NOS) refers to malignant tumours with glandular or ductal differentiation that do not have specific histologically defining features to enable further sub-classification as a recognized subtype.





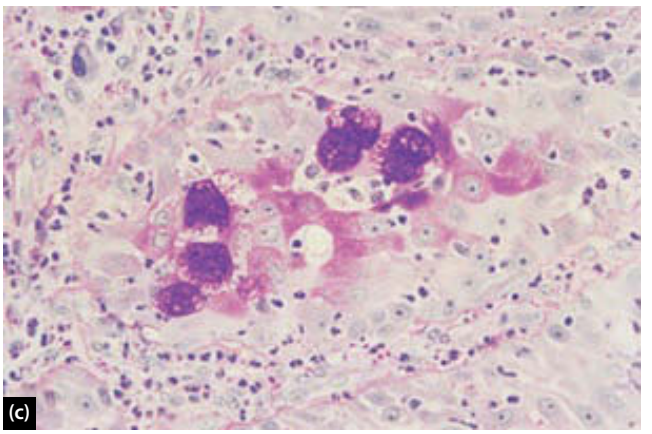


Figure 26.13 Mucoepidermoid carcinoma. **(a)** Whole mount slide of a low-grade mucoepidermoid carcinoma illustrating an expansile multilobulated architecture, substantial macrocystic and microcystic growth plus peripheral lymphoid tissue response (H&E stain, ultralow magnification). **(b)** Intermediate-grade tumour depicting epidermoid cells surrounding a rudimentary tubuloductal lumen lined by goblet cell mucocytes, characterized by abundant microvacuolated cytoplasm (H&E stain, high magnification). **(c)** The same tumour stained for neutral mucosubstances demonstrates mucocytes (dPAS stain, high magnification).

TABLE 26.7 Grading system for mucoepidermoid carcinoma[39]

Parameter	Point value	
Intracystic component <20%	2	
Neural invasion	2	
Necrosis	3	
Mitoses (>4 per 10 HPF)	3	
Anaplasia	4	
Grade	**Total score**	**Overall survival (10 years)**
Low	0–4	90%
Intermediate	5–6	70%
High	7–14	25%

HPF, high power fields.

Epidemiology

Adenocarcinoma NOS is the third most common malignant salivary gland neoplasm. It is more common in women and frequently seen in the fifth to eighth decade with a mean age of diagnosis of 58 years, and it is rarely seen in adolescents or children. Sixty per cent occur in the major salivary glands, usually the parotid, and 40% occur in the minor salivary glands.[11–13]

TABLE 26.8 Growth patterns of acinic cell carcinoma[11, 12]

Growth pattern	Features
Solid	Cells aggregate into sheets forming lobules or nodules
Microcystic	The tumour has a sieve-like appearance due to the presence of microcysts
Papillary–cystic	The tumour contains prominent cysts with intraluminal papillary projections
Follicular	Contain multiple variable-sized cysts loosely resembling thyroid parenchyma

Macroscopic appearance

Macroscopically, tumours appear as a firm tan-white mass, which can be circumscribed to poorly demarcated with an irregular periphery and potentially infiltrative appearance. There may be areas of haemorrhage, cystic change or necrosis.

Microscopic appearance

Adenocarcinoma NOS is a diagnosis of exclusion and therefore tumours that fall within this category can display a variety of features. Common to all tumours in this group is the presence of glandular or ductal features, an invasive

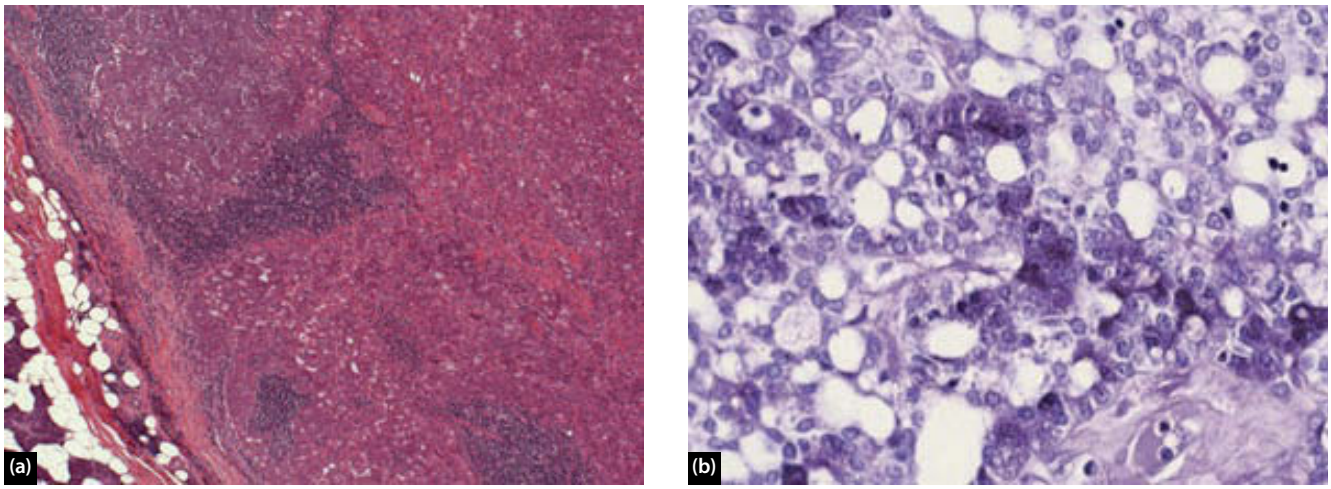


Figure 26.14 Acinic cell carcinoma. **(a)** Sheets of serous acinar cells arranged in a lobular pattern, note the lymphoid stroma (H&E stain, low magnification). **(b)** Microcystic pattern acinic cell carcinoma, there are a few serous acinar secretory cells containing purple zymogen granules (dPAS stain, high magnification).

growth pattern and the lack of histological characteristics of other salivary adenocarcinomas. The malignant epithelium can display various architectural features including glandular, ductal, papillary, solid and nest-like. There may be clear cell change and/or mucinous differentiation. The tumours can also be graded into low, intermediate and high, based on the degree of gland formation, cellular pleomorphism and mitotic count:

- Low-grade tumours have easily identifiable gland and duct-like structures. There is usually a single cell type with small nucleoli, abundant cytoplasm, distinct cell borders and little nuclear pleomorphism with few mitoses. This can occasionally lead to a benign diagnosis if the invasive growth is not identified.
- Intermediate-grade tumours also have easily identified gland and duct-like structures. Unlike low-grade tumours, there is greater nuclear pleomorphism with more mitoses.
- High-grade tumours tend to be solid, with areas of haemorrhage and necrosis. Unlike low- and intermediate-grade tumours, the gland and duct-like structures are much sparser. The cells are much more abnormal and varied. Cellular features include frequent atypical mitoses and enlarged, hyperchromatic, pleomorphic nuclei.

ADENOID CYSTIC CARCINOMA

Epidemiology

Adenoid cystic carcinoma (ACC) accounts for approximately 10–12% of all malignant salivary gland tumours and is the most common malignant tumour of the submandibular gland. It represents approximately 5% of parotid neoplasms and 30–50% of minor salivary gland neoplasms. There is no sex predilection and it is usually seen in patients in their 40s to 60s, rarely in patients under 20 years old. [11–13]

Macroscopic appearance

The tumour is usually a poorly circumscribed solid white tumour. ACC infiltrates into surrounding soft tissue, muscle and bone, sometimes directly through lymph node capsules.

Microscopic appearance

There are often two recognizable malignant cell subpopulations representing epithelial and myoepithelial components. Three growth patterns have been described but many tumours are mixed.

Tubular pattern represents the most differentiated form of ACC.[41] Small nests of cells form few true glandular or tubule-ductal spaces and occasional cords.

Cribriform pattern is the most common pattern and most tumours will contain areas displaying this pattern even if not the predominant type. In addition to true gland lumina containing secretions, cells group to form multiple pseudocysts (pseudolumina) containing mucoid basement membrane material. The overall pattern resembles 'Swiss cheese' (**Figure 26.15**). This architecture represents an intermediate level of cellular proliferation and biological aggressiveness.[41]

Solid pattern is the least common type and unlike the other two types there are few glandular spaces. Cells in the solid type tend to be larger and more pleomorphic with mitoses, interspersed with areas of necrosis. A biphasic cell population may not be apparent and without at least some better-differentiated fields, it may be impossible to arrive at the diagnosis.

ACC may be graded according to the predominant growth pattern:[11–13]

- Grade I, mostly tubular with some cribriform elements
- Grade II, either entirely cribriform or cribriform/tubular with less than 30% solid component
- Grade III, any tumour with more than 30% solid growth.

Low-grade ACC pursues a pernicious course typified by relentless, troublesome local recurrence, ultimately presaging

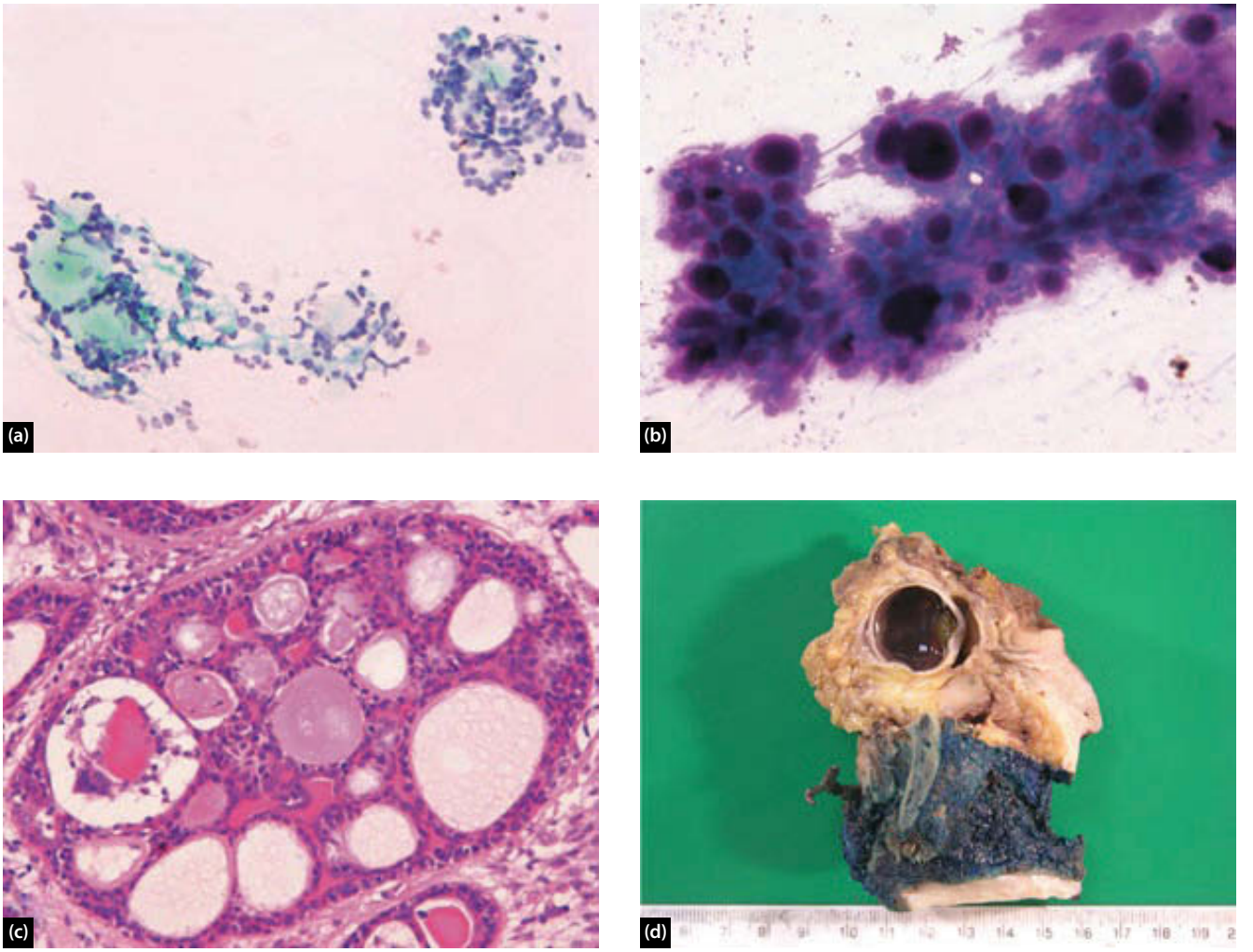


Figure 26.15 Adenoid cystic carcinoma (ACC). **(a)** FNAB illustrating cribriform microbiopsies. The characteristic hyaline basement membrane globules are pale in this preparation (Pap stain, medium magnification). **(b)** Cytology showing similar features albeit with striking intense staining of the hyaline globules (May–Grunwald-Giemsa (MGG) stain, medium magnification). **(c)** Classical cribriform ACC demonstrating pseudolumina filled with variably dense basement membrane type droplets, together with true gland lumina, either empty or containing sparse secretions (H&E stain, high magnification). **(d)** Right maxillectomy and orbital exenteration, for recurrent ACC.

wider dissemination after a prolonged interval of years or even decades. Many malignant salivary gland tumours show a propensity for perineural growth, though this is characteristic for ACC, the latter commonly visualized microscopically some considerable distance beyond what would be regarded as adequate surgical clearance. This neurotropism may radiate in a tentacular fashion well beyond the main body of the tumour. Positive surgical resection planes are, therefore, sometimes an unexpected and unwelcome feature of pathology reports, as this signifies inevitable local recurrence. Obversely, the histological suggestion of surgical clearance is not particularly reassuring. High-grade (solid) ACC is an aggressive, destructive malignancy.

CARCINOMA EX PLEOMORPHIC SALIVARY ADENOMA

Carcinoma ex-pleomorphic adenoma arises from within a pre-existing PSA or at the site of a previous pleomorphic adenoma.

Epidemiology

Carcinoma ex-pleomorphic adenoma is not uncommon and accounts for approximately 12% of all salivary gland malignancies and 6.2% of all pleomorphic adenomas.[42] Risk factors for malignant transformation of a pleomorphic adenoma include older age of patient (mean, 61 years), male sex, prolonged duration of tumour and multiple recurrences.[12, 43] It commonly affects the parotid gland and, rarely, the sublingual gland.

Macroscopic appearance

Carcinoma ex-pleomorphic adenoma tends to be larger than its benign counterpart. Tumours tend to be poorly circumscribed, firm, tan-white and extensively infiltrative masses. They can occasionally be well circumscribed and appear encapsulated. The 'ghost' of a pre-existing adenoma is often identified, sometimes alluded to by a dense, occasionally mineralized, scar. The malignant component tends to radiate centrifugally from this nidus, if present (**Figure 26.16**).

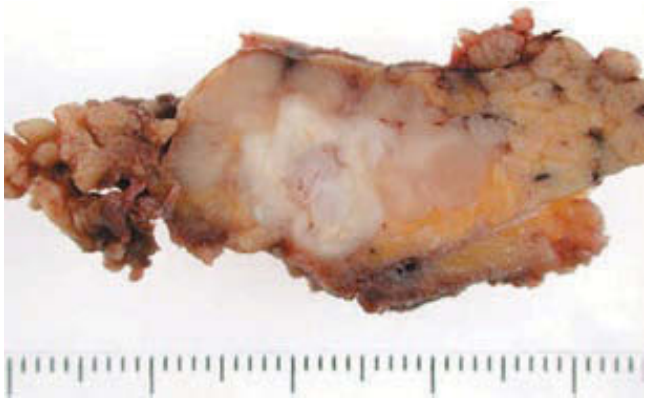


Figure 26.16 Carcinoma ex-pleomorphic salivary adenoma. Cut surface of a longstanding adenoma seen centrally forming a discrete, cream, elastotic scar with focal calcification. This is part-circumferentially surrounded by peripheral lobules of tan carcinoma ex-adenoma.

Microscopic appearance

The malignant element of a carcinoma ex-pleomorphic adenoma typically comprises high-grade adenocarcinoma or salivary duct carcinoma often with squamoid differentiation, but other specific subtypes of salivary carcinoma are seen and these may on occasion be monotypic rather than mixed. The benign pleomorphic adenoma component can be difficult to identify, may require extensive sampling and in some cases it may never be identified. The association of pleomorphic adenoma, carcinoma and sarcoma (carcinosarcoma, true malignant mixed tumour) is very rare. Invasion of tumour through the original lesion's capsule carries prognostic significance and has been classified as:[11–13]

1. Intracapsular carcinoma
2. Minimally invasive carcinoma (less than 4–6 mm invasion)
3. Widely invasive carcinoma.

In principle, (1) and (2) have a favourable prognosis compared to (3), although the precise cut-off point to define a category of invasion with minimal metastatic potential is controversial. Ordinarily, pleomorphic adenomas may show peripheral permeative growth, lymphatic tumour embolus, necrosis and focal internal cytonuclear atypia without signifying malignant transformation. Caution should be exercised in the interpretation of such features if prior FNAB has been attempted. Such tumours are sometimes termed 'atypical pleomorphic adenoma' and generally behave no differently from their more typical counterparts.

MOLECULAR PATHOLOGY OF SALIVARY GLAND TUMOURS

In recent years, a number of genetic alterations have been associated with salivary gland neoplasms.[12] Specifically, the presence of chromosomal translocations and their gene fusions have been used to aid diagnosis (**Table 26.9**).

TABLE 26.9 Chromosomal translocations in salivary gland tumours[12]

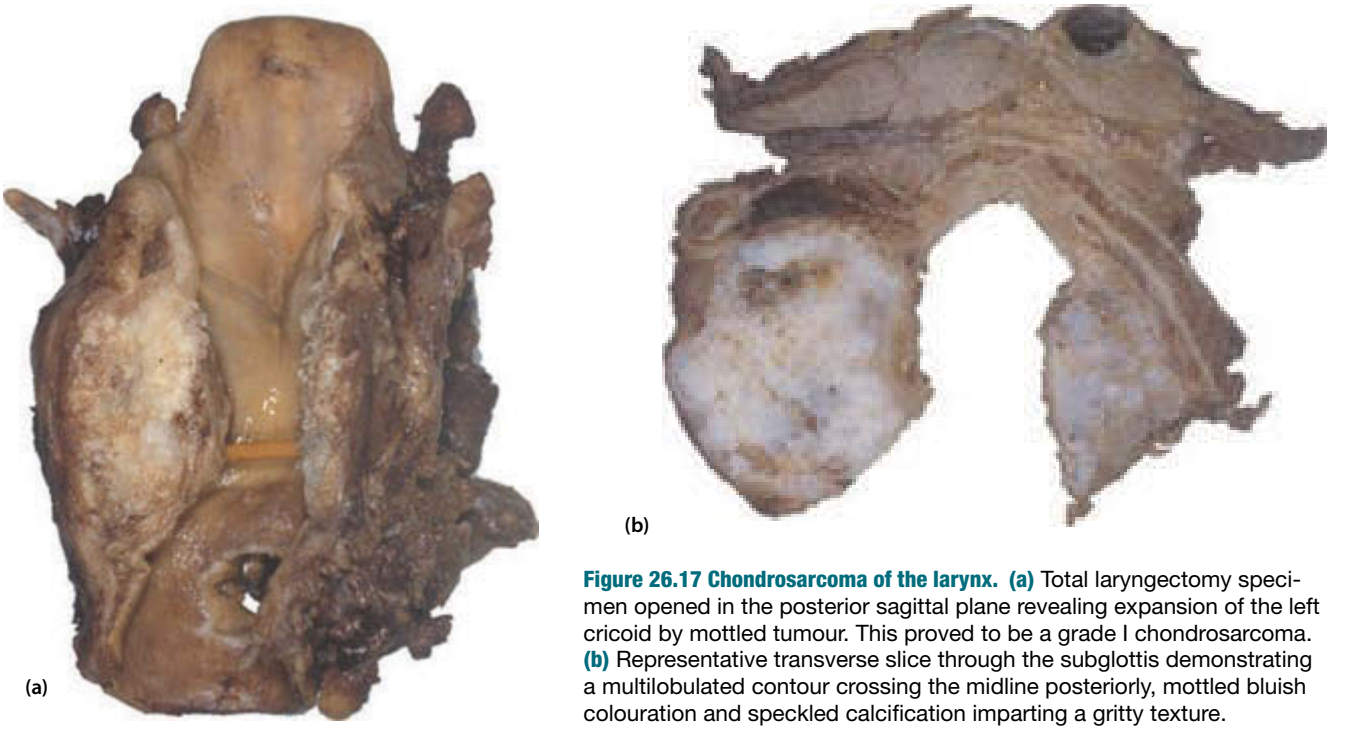
Salivary tumour	Fusion oncogene	Diagnostic utility
Pleomorphic adenoma	PLAG-1 fused to CTNNB1, TCEA1 or others	*PLAG-1* abnormality in 30% of tumours
Mucoepidermoid carcinoma	CRTC1-MAML2 (>80%) CRTC3-MAML2 (<10%)	Present in low and intermediate grade tumours
Adenoid cystic carcinoma	MYB-NFIB MYBL1-NFIB	Present 80–90% of tumours
Secretory carcinoma	ETV6-NTRK3	Defines the entity

These molecular alterations can be detected by fluorescence *in situ* hybridization (FISH), PCR or DNA sequencing. Recently, secretory carcinoma, a low grade salivary gland carcinoma, has been described and is defined by a translocation (12;15)(p13;q25) leading to formation of an ETV6-NTRK3 fusion oncogene. In the past, these cases were likely diagnosed as acinic cell carcinomas. It is hoped that such molecular information will facilitate accurate diagnosis and produce new insights into the management of these interesting and rare tumours.

Lymphomas

Lymphoma is the second most common primary malignancy occurring in the head and neck region. Approximately 25% of all extra-nodal lymphomas occur in the head and neck. Thus, although in the UK the overwhelming majority of haematolymphoid tumours, predominantly lymphomas and leukaemias, are managed by specialist haemato-oncology multidisciplinary teams, head and neck surgeons are frequently involved in the initial diagnosis of lymphoma. It is, therefore, important that the head and neck pathologist possesses a sound working knowledge of lymphoproliferative conditions and their differential diagnosis.

It is beyond the scope of this chapter to delve into the complexities of lymphoma diagnosis and the interested reader is referred to the comprehensive World Health Organisation (WHO) classification of tumours of haematopoietic and lymphoid tissues (4th edition, 2008), which is internationally recognized, periodically reviewed and updated.[44,45] This takes a multiparameter approach to classification incorporating clinical, morphological and immunophenotypical features plus genetic studies into account with the expectation that the schema will continually evolve and be refined over time. Lymphomas are broadly divided into Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL). HL is characterized by Reed–Sternberg cells and is subdivided into classical HL (incorporating nodular sclerosing, mixed cellularity, lymphocyte-rich and lymphocyte-depleted subtypes) and nodular lymphocyte predominant HL, according to site of involvement, clinical features, growth pattern, presence of fibrosis, composition of cellular background, number and/or degree of atypia



(a) (b)

Figure 26.17 Chondrosarcoma of the larynx. (a) Total laryngectomy specimen opened in the posterior sagittal plane revealing expansion of the left cricoid by mottled tumour. This proved to be a grade I chondrosarcoma. **(b)** Representative transverse slice through the subglottis demonstrating a multilobulated contour crossing the midline posteriorly, mottled bluish colouration and speckled calcification imparting a gritty texture.

of the tumour cells and frequency of EBV infection. The immunophenotype of the neoplastic cells in these classical HL subtypes is identical. Around 85% of NHLs are B-cell lymphomas, which include chronic lymphocytic leukaemia/small lymphocytic lymphoma, follicular lymphoma, marginal zone lymphoma, the latter often extranodal involving the mucosa-associated lymphoid tissue of Waldeyer's ring. Diffuse large B-cell lymphoma is the most common aggressive NHL. Mantle cell lymphoma and Burkitt lymphoma are aggressive NHLs sometimes seen in the head and neck region. Plasma cell neoplasms, most commonly plasma cell myeloma and extramedullary plasmacytoma, are occasionally encountered in the head and neck region. Cutaneous T-cell NHLs (e.g. mycosis fungoides) may affect head and neck skin, but are rarely seen at mucosal sites. Extra-nodal NK/T-cell lymphoma is strongly associated with EBV infection and shows a predilection for the upper aero-digestive tract, typically the nasal cavity. Its angiocentric and angio-destructive nature may mimic the histological features of granulomatosis with polyangitis.

Malignant mesenchymal tumours

Malignant mesenchymal tumours (sarcomas) are uncommon in the head and neck region, but include:

- fibrosarcoma
- malignant fibrous histiocytoma
- leiomyosarcoma
- rhabdomyosarcoma
- liposarcoma
- angiosarcoma
- Kaposi sarcoma
- malignant peripheral nerve sheath tumour
- synovial sarcoma
- chondrosarcoma (**Figure 26.17**)
- mesenchymal chondrosarcoma
- osteosarcoma
- chordoma.

Neuroectodermal tumours

MUCOSAL MALIGNANT MELANOMA

Mucosal malignant melanoma is a rare tumour that originates from neuroectodermal-derived melanocytes.[46] Between 15% and 20% of malignant melanomas arise in the head and neck region, but the vast majority, over 80%, are of cutaneous or upper aerodigestive tract origin. Mucosal malignant melanoma represents merely 0.5–3% of malignant melanomas from all sites.[10] Common sites for mucosal malignant melanoma include the sinonasal tract and the oral cavity, particularly the palate. It is more common in men, but this finding is not consistent, and the tumour affects a wide age range (20–80 years).

Macroscopic appearance

Mucosal melanomas are usually pigmented and colour ranges from a light tan to black depending on the amount of melanin production, though amelanotic examples do occur.

TABLE 26.10 Hyams' grading classification of olfactory neuroblastoma[14]

Histological feature	Grade I	Grade II	Grade III	Grade IV
Architecture	Lobular	Lobular	May be lobular	May be lobular
Mitoses	Absent	Present	Prominent	Marked
Nuclear pleomorphism	Absent	Present	Prominent	Marked
Neurofibrillary matrix	Prominent	Present	May be present	Absent
Rosettes	Homer–Wright rosettes	Homer–Wright rosettes	Flexner–Wintersteiner rosettes	Flexner–Wintersteiner rosettes
Necrosis	Absent	Absent	Present	Prominent

Microscopic appearance

They typically comprise epithelioid and/or spindle cells. Plasmacytoid, rhabdoid, small cell, giant cell, balloon cell, neurotropic and desmoplastic variants are recognized. The cells are markedly pleomorphic and may contain pigment. Nucleoli are conspicuous and intra-nuclear inclusions are typical. An adjacent inflammatory infiltrate and necrosis can also be present. Melanocytic atypia or melanoma *in situ* may be observed in the background mucosa.

With few exceptions, the cells show nuclear and cytoplasmic immunoreactivity for S100 protein. MelanA, HMB-45 and SOX10 are usually positive. Epithelial markers are negative, although up to 10% of melanomas may show focal cytokeratin reactivity. The desmoplastic variant of melanoma may be negative for all these markers. Mucosal melanomas usually do not harbour BRAF v600E mutations and consequently are unlikely to benefit from vemurafenib targeted treatment.[12]

OLFACTORY NEUROBLASTOMA

These are uncommon malignant tumours of the upper nasal cavity affecting specialized olfactory mucosa and arising from the superior turbinate, cribriform plate and superior one third of the nasal septum. The reported incidence is four cases per million with a bi-modal distribution in the second and sixth decade, and no sex or racial predeliction.[12]

Macroscopic appearance

Macroscopically, olfactory neuroblastoma appears as a soft, polypoidal, highly vascular mucosa-covered mass.

Microscopic appearance

The malignant cells are uniform, with small round nuclei, scant cytoplasm and possess finely stippled (salt and pepper) chromatin. Hyams' classification system divides olfactory neuroblastoma into four types (**Table 26.10**).[14] The better-differentiated (grade I and II) examples are sometimes termed 'aesthesioneuroblastoma'. Homer–Wright pseudorosettes are formed by cells mantling

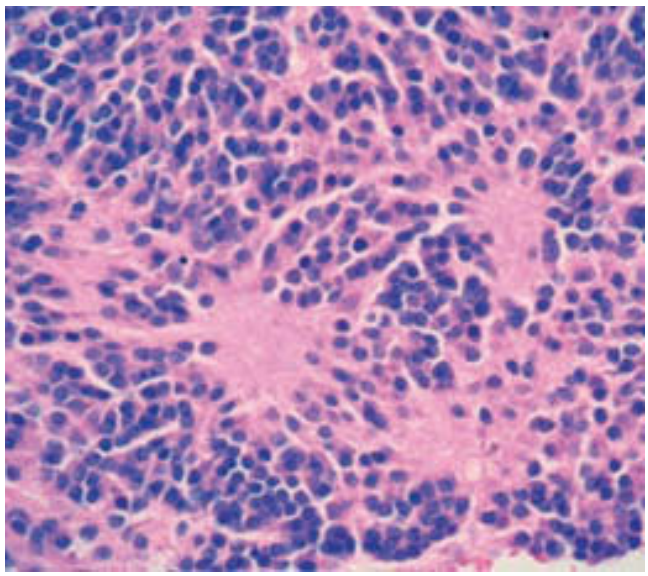


Figure 26.18 Grade I/II olfactory neuroblastoma. Loosely cohesive, uniform, small cells including two Homer–Wright pseudorosettes centred on fibrillary neuropil material. Mitoses are inconspicuous. There is no necrosis (H&E stain, high magnification).

solid, fibrillary neuropil stroma (**Figure 26.18**). Flexner–Wintersteiner rosettes consist of cells surrounding an empty pseudolumen. Other tumours may form perivascular rosettes encircling blood vessel lumina. IHC may aid discrimination between this and other primitive neoplasms (so-called round blue cell tumours), such as lymphoma, Ewing's tumour, melanoma, Merkel cell tumour, rhabdomyosarcoma, nephroblastoma, retinoblastoma and primitive neuroectodermal tumour (PNET).[47] There is, however, no single specific positive marker.

Metastases to the head and neck region

Uncommonly, a primary tumour at another body site may metastasize to the head and neck region. The most commonly encountered are carcinomas of the lung, colon, breast, prostate and kidney (**Figure 26.19**).[11]

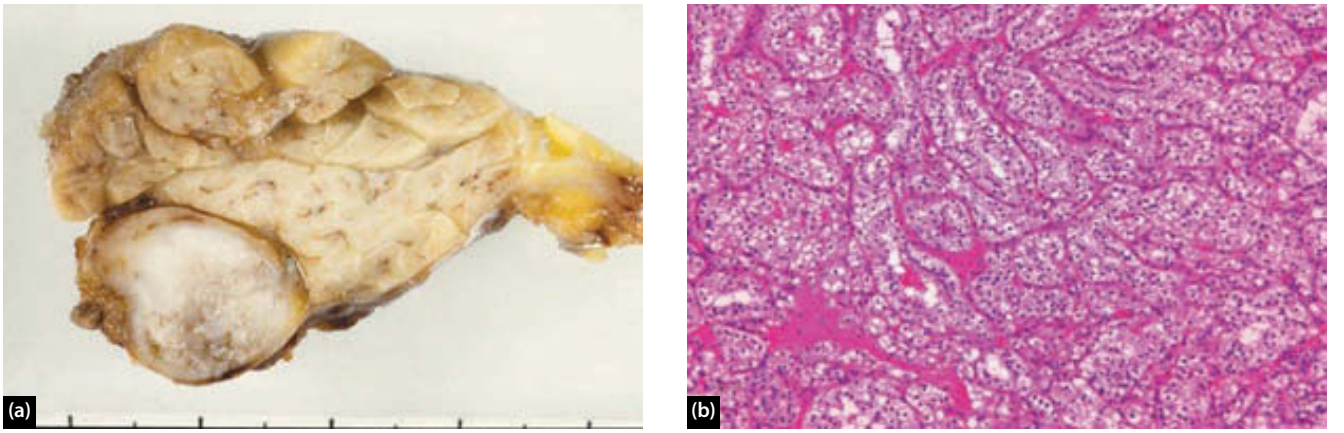


Figure 26.19 Metastatic disease in the head and neck. **(a)** Cut surface of a metastatic deposit effacing a para-parotid lymph node. **(b)** Metastatic clear cell carcinoma from an occult renal primary tumour (H&E stain, medium magnification).

KEY POINTS

- Meticulous and judicious pathological evaluation of head and neck biopsies is essential for effective clinical management.
- Morphological assessment by light microscopy constitutes the cornerstone of cytological and histological diagnosis, supplemented by immunohistochemical and molecular tests, where relevant.
- Fine-needle aspiration biopsy (FNAB) is a comparatively low-risk, cost-effective preliminary investigation in the management of head and neck lumps.
- The histocytopathological diagnostic process is historically heuristic in nature, correlating clinical, pathological, radiological and treatment outcome observations using population and individual case study evidence.
- The head and neck pathologist must be an accomplished practitioner familiar with perhaps the widest range of organ/tissue-specific diseases out of all the anatomically defined site-specific specialities.
- Tumour site, type, grade and stage are major determinants of survival in head and neck cancer, which is influenced to a lesser degree by a variety of other patient-specific and tumour-specific factors. These are accommodated in the UICC/AJCC TNM classification.
- Squamous cell carcinoma in its numerous manifestations accounts for upwards of 90% of all malignant head and neck tumours with lymphoma as the second most common malignancy.
- Fine-needle aspiration biopsy (FNAB) is an established first-line investigation for suspected head and neck cancer. It is rapid, comparatively atraumatic, requires minimal specialized equipment and in experienced hands offers good clinical efficiency, as long as awareness of its inherent limitations and pitfalls is maintained by all concerned.
- The application of immunohistochemistry and molecular markers with deeper understanding of their genetic basis continues to yield insight into the pathogenesis of many head and neck tumours. Their routine use in diagnosis, treatment and prognostication is likely to become more widespread in the future.

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CHAPTER 27

OPEN CONSERVATION SURGERY FOR LARYNGEAL CANCER

Volkert Wreesmann, Jatin Shah and Ian Ganly

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SEARCH STRATEGY

Data in this chapter may be updated by a searching using the following keywords: laryngeal squamous cell carcinoma, conservation laryngeal surgery, laryngeal preservation and functional outcome.

INTRODUCTION

Cancer of the larynx is a debilitating disease associated with significant functional morbidity (breathing, speech, swallowing) and mortality. The preferred treatment choice for laryngeal cancer patients provides the optimal balance between disease control prospects and likelihood of treatment-related functional, aesthetic and psychological side effects.[1] Total laryngectomy (TL) with or without post-operative radiation treatment (PORT) offers the best chances for cure across all types and stages of laryngeal cancer.[2] However, TL is associated with severe functional sequela (**Table 27.1**), significant reduction in quality of life (QOL) and low patient acceptance. As such, it is now mostly applied to clinical scenarios in which TL is the sole viable treatment option, such as advanced (T4a) tumour stage, or in cases of locally recurrent disease after radiation treatment. The majority of laryngeal cancers can be treated with more conservative treatment alternatives that provide an improved risk-benefit ratio compared to TL.[3]

Primary radiation therapy can be applied for definitive treatment of early (T-stage 1/2) laryngeal cancers, yielding local control and larynx preservation rates of 85–95%, acceptable voice outcomes, and the possibility for surgical salvage in cases of failure.[4] However, in advanced stage III/IV laryngeal cancer, its efficacy is considered too low (40% local control), even in the setting of intensified radiotherapy protocols (accelerated, hyperfractionated, or intensity-modulated RTx).[5] The efficacy of radiation therapy for advanced laryngeal cancer can be improved significantly with the addition of cisplatin-based chemotherapy.[5] Evidence from several randomized controlled trials suggests that chemoradiation treatment of advanced laryngeal cancer provides control rates that approximate those of TL, while larynx preservation can be achieved in 66–84% of these patients.[5,6] Although the introduction of primary (chemo) radiation has revolutionized the treatment of laryngeal cancer, increasing follow-up data demonstrate a progressive accumulation of significant treatment sequela over time.[7,8] These include laryngeal oedema, fibrosis,

TABLE 27.1 Sequela of total laryngectomy

Communication	• Loss of normal speech quality and quantity
Airway closure	• Loss of airway protection • Loss of effective cough • Loss of ability to strain
Nasal airflow	• Loss of nasal air conditioning • Loss of smell and taste • Loss of normal nasal homestasis and immunity
Swallowing	• Loss of normal constrictor muscle anatomy • Loss of normal sensory and motor innervation • Fibrosis of constrictor muscles • Loss of upper esophageal sphincter
Psychological	• Body image issues with stoma

TABLE 27.2 Comparison open partial laryngectomy (OPL) and transoral laser microscopic laryngectomy (TLM) and (chemo)radiotherapy (C)RTx for laryngeal cancer

	OPL	TLM	(C)RTx
Oncologic results	Equivocal	Equivocal	Equivocal
Speech quality	Poor	Good	Good
Swallowing	Normal	Normal	Impaired
Complications	Respiratory	Rare	GI ,respiratory, systemic
Feeding tube	Temporary – 1 month	No	5–10%
Tracheostomy	Temporary – 1 month	No	Occasional
Treatment duration	1 day	1 day	7 weeks
Costs	Medium cost	Low cost	Expensive
Repeated treatment	No. Only salvage TL or RT	Yes. Repeated laser possible	No. Only salvage TL

laryngeal neuropathy, dysphagia, vocal cord (VC) dysfunction and airway insufficiency. Surgical salvage is required in a significant number of cases with these complications.

Conservation partial laryngeal surgery may provide the best balance between cure and complications for a significant proportion of laryngeal cancer cases.[2, 9] Traditional partial laryngeal surgery is performed through an open transcervical approach, but recent technical developments (refinement of medical laser applications, introduction of endoscopes, microscopes and image guidance systems) have led to the development of less invasive transoral laser microsurgery (TLM) (**Table 27.2**). In early laryngeal cancers, partial laryngectomy provides local control and laryngeal preservation (LP) rates that are at least equivalent to primary radiation therapy, and acceptable functional outcome.[9] In advanced laryngeal carcinomas, open partial laryngectomy can be applied in selected cases and the role of TLM is increasing, both showing oncologic and functional efficacy that may outperform chemoradiation.[9] With appropriate patient selection, partial laryngectomy can be applied in approximately 30–50% of radiorecurrent laryngeal cancers as well, providing surgical salvage and avoiding TL in these patients.[10] Although transoral laser surgery has now largely replaced open partial laryngectomy, several indications for open partial laryngectomy remain, and mandate comprehension and inclusion into the armamentarium of the head and neck surgeon. This chapter will focus on the open conservation surgical approaches for laryngeal cancer, while transoral laser partial laryngectomy will be discussed in Chapter 23, Anatomy as applied to transoral surgery.

SURGICAL GOALS OF OPEN PARTIAL LARYNGECTOMY

The goal of open partial laryngectomy is complete tumour removal, while preserving the functional integrity and separation of larynx and pharynx. This delicate balance requires a detailed understanding of anatomical relationships, a high level of surgical finesse and familiarity with different conservational surgical options, as well as experience on the part of the surgeon.

Complete tumour removal is defined by acquisition of microscopically negative margins of resection upon pathological examination. Chances of local control are decreased significantly in the absence of pathologically negative margins after conservation laryngeal surgery. Survival may be compromised in this setting as well, as the altered post-surgical anatomy and tissue plane boundaries both facilitate unconventional tumour spread, and hamper early detection of tumour recurrence, making salvage treatment more complicated. In recurrent laryngeal cancers after (chemo)radiation, microscopic complete tumour removal is clearly critical, as adjuvant treatment options are limited. In radiation-naive laryngeal cancers amenable to conservation laryngeal surgery, the treatment plan is generally geared towards avoidance of alternative larynx preservation strategies including primary (chemo) radiation treatment and its sequelae, and this focus can only be maintained upon confirmed negative margins. For these reasons, conservation laryngeal surgery should only be attempted when acquisition of negative margins can be anticipated with confidence.

Successful functional outcome after conservation laryngeal surgery is dependent on three factors that need to be addressed during surgery: (i) establishment of an adequate airway with functional (neo)glottic valve; (ii) recreation of adequate post-operative pharyngeal anatomy for optimal swallowing; and (iii) maintenance of an optimal laryngopharyngeal coordination between motor input and sensory feedback to guarantee airway protection and adequate swallowing.[12] Airway patency after conservation laryngeal surgery may be reduced due to post-operative oedema, fibrosis, redundant mucosa and poorly positioned laryngopharyngeal anatomical constituents, all of which may lead to delayed decannulation, upper and lower airway complications, and need for reoperation. All of these potential issues need to be carefully addressed during surgery and in the post-operative period. Moreover, preservation of a competent (neo)glottic valve is critical for

successful conservation surgery, as it decreases aspiration, improves subglottic pressures and coughing ability, and optimizes speech.

The cricoarytenoid unit is the basic functional unit of the larynx. The cricoarytenoid unit consists of an arytenoid cartilage, the cricoid cartilage, the associated musculature and the nerve supply from the superior and RLNs for that unit. It is the cricoarytenoid unit, not the vocal folds, that allows for physiologic speech and swallowing without the need for a tracheostoma. Preservation of at least one functional unit allows organ preservation laryngeal surgery.[11] Careful preservation of the RLN, which can be placed at risk during dissection in the area of the cricothyroid joint, is one critical aspect of an intact cricoarytenoid unit. Scarring in and around the cricoarytenoid joint should be prevented, as it increases chances for arytenoid fixation. Also, scarring of key intrinsic laryngeal muscles such as the lateral cricoarytenoid muscle should be prevented. In some cases, arytenoid resuspension may be necessary to optimize its anatomical position.

Optimal pharyngeal anatomy is critical for successful swallowing after partial laryngectomy, and although this is in part dependent on wound healing, it can be influenced intra-operatively. Important aspects of this goal are optimal resuspension of the larynx to the tongue base, in a fashion that takes into account the delicate balance between airway protection by a posteriorly 'overhanging' tongue base and airway obstruction by the same. In addition, the shape and position of the pyriform sinuses are vital to unobstructed food passage and reduction of aspiration risk. The normal configuration of the pyrifom sinuses is disrupted by partial laryngectomy and often, resuspension of the pyriform sinuses is needed. This recreates the anatomic funnel shape of the hypopharyngeal inlet and decreases the chance for obstruction by redundant mucosa after the procedure. Cricopharyngeal myotomy can further help facilitate unobstructed food passage and can be considered in case the constrictor lumen feels narrow on finger dilatation.

Proper neurological coordination is also vital for adequate swallowing, not only in terms of intact motor function of swallowing muscles but also in terms of intact sensory feedback of the passing food bolus. Therefore, a detailed knowledge of the neurological anatomy is critical for surgical success. The bulk of laryngopharyngeal sensation above the VCs is provided by the inner branches of the SLNs. These enter the laryngopharynx through the thyrohyoid membrane and, once inside, run in the pharyngoepiglottic fold from lateral to medial direction. Next, they give off two major branches on each side of the larynx, which run in the laryngopharyngeal submucosa in an inferior direction towards the pyriform sinuses and VCs and form an anastomosing bilateral network. Although many laryngeal extensions of the SLN will be sacrificed during partial laryngectomy, great care should be taken to leave the main trunk of the nerve, and the pharyngeal extensions intact. During partial laryngectomy, there are several procedural steps at which the SLN may be at risk. These include: (i) separating infrahyoid muscles from hyoid, in which too much lateral dissection will damage the nerve; (ii) trans-vallecular pharyngotomy, in which too much lateral dissection will damage the nerve; (iii) freeing the superior horn of the thyroid cartilage where the SLN lies just superolateral to the tip of the thyroid horn; and (iv) releasing inferior constrictor and pyriform sinus mucosa from the paraglottic space. Experience and careful surgical technique contribute significantly to optimized functional outcome after partial laryngectomy.[12]

TYPES OF OPEN PARTIAL LARYNGECTOMY

Open partial laryngectomy was first performed by Theodor Billroth in 1874, and several different modifications have since been developed. These procedures can be applied to both glottic and supraglottic disease, and they include vertical and horizontal oriented procedures. Procedures that can be applied to glottic disease include several vertical hemilaryngectomy modifications and horizontal supracricoid laryngectomy with cricohyodoepiglottopexy (CHEP). For supraglottic disease, supraglottic laryngectomy and supracricoid laryngectomy with cricohyoidopexy (CHP) have been developed, both of which are horizontally oriented procedures.

Vertical partial laryngectomy

This procedure may be an anterolateral, frontolateral or anterior vertical partial laryngectomy.

ANTEROLATERAL HEMILARYNGECTOMY

Anterolateral hemilaryngectomy has been developed for glottic tumours that do not involve the anterior commissure. This procedure involves exposure of the thyroid cartilage below the strap muscles, and the ipsilateral perichondrium overlying the thyroid cartilage is lifted in order to preserve it. Next, vertical cuts through the laryngeal cartilage in a midline laryngofissure fashion are performed (**Figure 27.1**). The majority of the ipsilateral thyroid cartilage, true VC, portions of the subglottic mucosa and false cord are removed. The extent of resection depends on the pre-operative and intra-operative assessment of tumour extent. The strap muscles are closed over the residual perichondrium to form a pseudocord. A tracheostomy and feeding tube are generally required for 3–7 days.

If the anterior commissure is involved, a frontolateral or anterior partial laryngectomy can be done.

FRONTOLATERAL HEMILARYNGECTOMY

In frontolateral vertical laryngectomy (**Figure 27.2**), the vertical cartilage cut in the thyroid is performed 1 cm paramedian from the anterior midline on the contralateral thyroid ala. This procedure is preferred if the tumour involves the VC on the ipsilateral side, the anterior commissure and up to one-third of the contralateral VC.

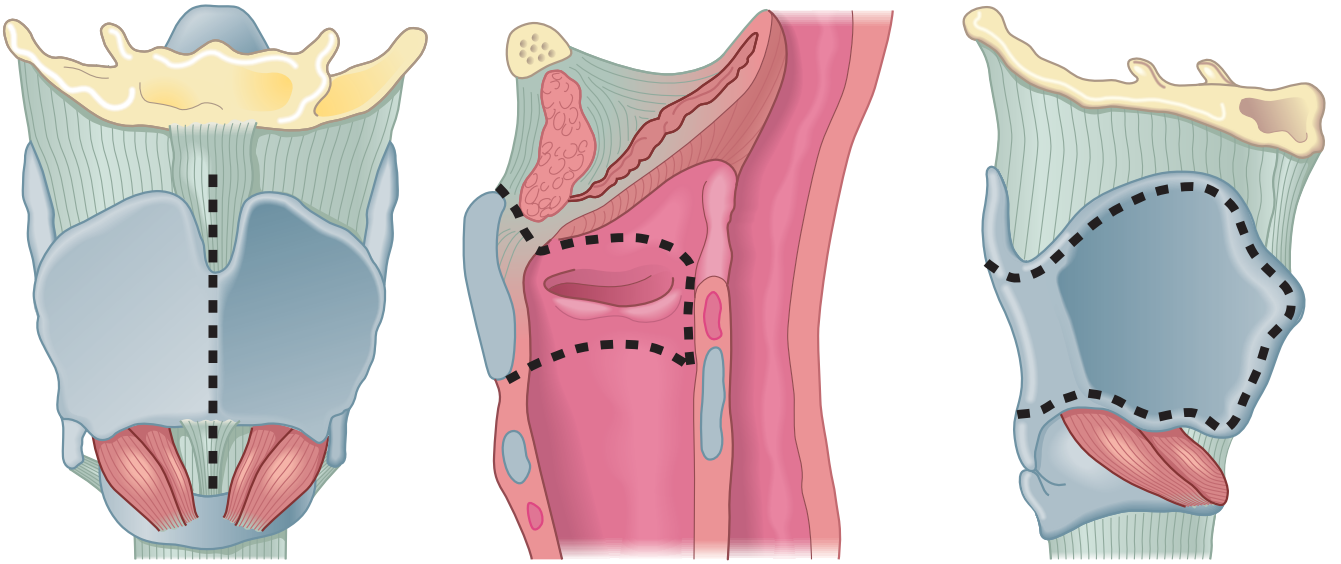

Figure 27.1 Anterolateral midline hemilaryngectomy.

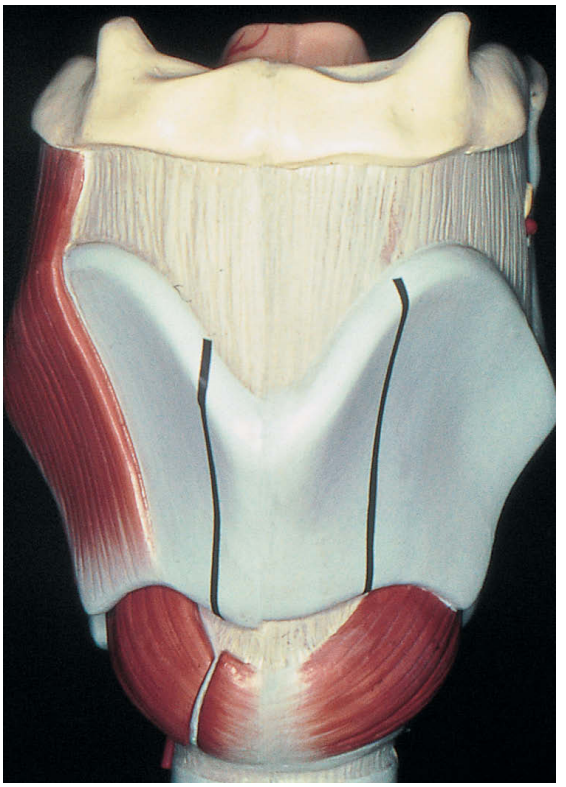

Figure 27.2 Frontolateral and anterior hemilaryngectomy.

Figure 27.3 Silastic keel.

ANTERIOR VERTICAL LARYNGECTOMY

Anterior vertical laryngectomy makes use of two paramedian thyroid cartilage incisions, each positioned approximately 1 cm paramedian from the anterior midline. This procedure may be preferred for an anterior commissure tumour that involves no more than the anterior third of one or both VCs. After tumour removal, the remnant posterior VCs are reattached to the anterior aspects of the remnant thyroid ala that are approximated in the midline. Formation of anterior laryngeal web is avoided with the use of a silastic keel, positioned at the anterior commissure between the VCs (**Figure 27.3**), which is removed endoscopically after 4 weeks.

Supracricoid partial laryngectomy (SCPL) with cricohyoidoepiglottopexy (CHEP)

Glottic tumours that extend across the midline through the anterior commissure are not suitable for vertical hemilaryngectomy if they involve more than the anterior third

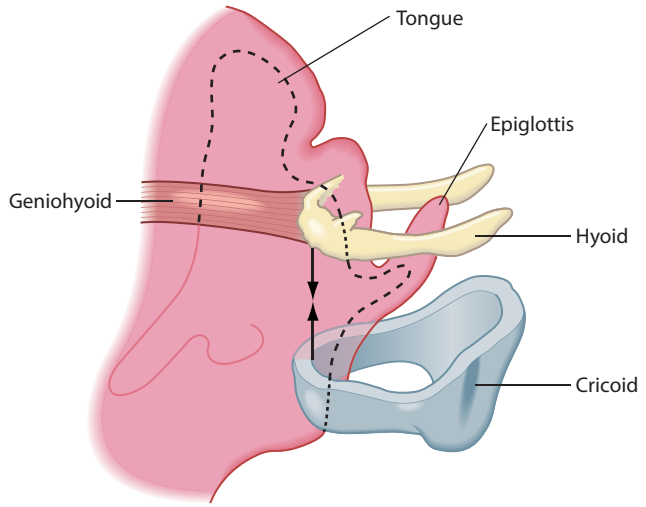

Figure 27.4 Supracricoid laryngectomy.

of the opposite VC. Supracricoid partial laryngectomy offers the possibility for resection of both true cords, both false cords, the entire thyroid cartilage, paraglottic spaces bilaterally, and a maximum of one arytenoid (**Figure 27.4**). Essential goals of this operation include careful preservation of the bilateral superior laryngeal nerves (SLNS) for optimal sensation during swallowing, functional preservation of at least one recurrent laryngeal nerve (RLN) for airway closure during attempted speech and swallowing, and adequate recreation of a functional neoglottic valve.[12, 13] The best functional results are achieved when both arytenoids are functionally and anatomically preserved. However, functional separation of the airway and the alimentary tract is possible provided at least one arytenoid is preserved.[14] Reconstruction is achieved by approximation of the hyoid bone to the cricoid with three absorbable sutures: one in the midline and two sutures placed 1 cm paramedian (to avoid suturing the lingual arteries, hypoglossal and SLN nerves). Also, the suprahyoid epiglottis is preserved and reapproximated to the cricohyoidopexia. Essential in the understanding of the post-operative functional status, is the fact that the orientation of the airway has undergone a 90% turn in the horizontal plane, from its anatomic slit-like antero-posterior orientation to a transverse or T-shaped orientation of the neoglottic valve. The latter can be closed sufficiently by the mobile arytenoid(s). A temporary tracheostomy is required, and most patients can be decannulated early. A nasogastric feeding tube is used in most patients, and can be removed in 4–6 weeks in most patients, provided that stringent swallowing therapy is in place. A PEG tube is advocated in older patients, patients with a single preserved arytenoid, patients with a history of radiation, or hypoglossal, SLN or RLN dysfunction. Quiet aspiration is present in most patients, and stringent oral hygiene is a prerequisite for pulmonary health.

Supracricoid partial laryngectomy (SCPL) with cricohyoidopexy (CHP) for supraglottic cancer

This operation is suitable for supraglottic carcinomas not amenable to horizontal supraglottic laryngectomy due to: (i) glottic level involvement through the anterior commissure or ventricle; (ii) pre-epiglottic space invasion; (iii) decreased cord mobility; (iv) limited thyroid cartilage invasion; or for glottic carcinomas with epiglottic or pre-epiglottic extension. The operation is essentially the same as described above, but an essential difference is the absence of the epiglottic remnant for reconstruction. Naturally, post-operative swallowing is delayed, and the rate and intensity of long-term aspiration is increased.

Horizontal supraglottic partial laryngectomy (HSPL)

In this procedure, the epiglottis, (part of the) hyoid bone, pre-epiglottic space, thyrohyoid membrane, upper half of the thyroid cartilage, aryepiglottic fold and part of the false cords are removed (**Figure 27.5**). The vallecula

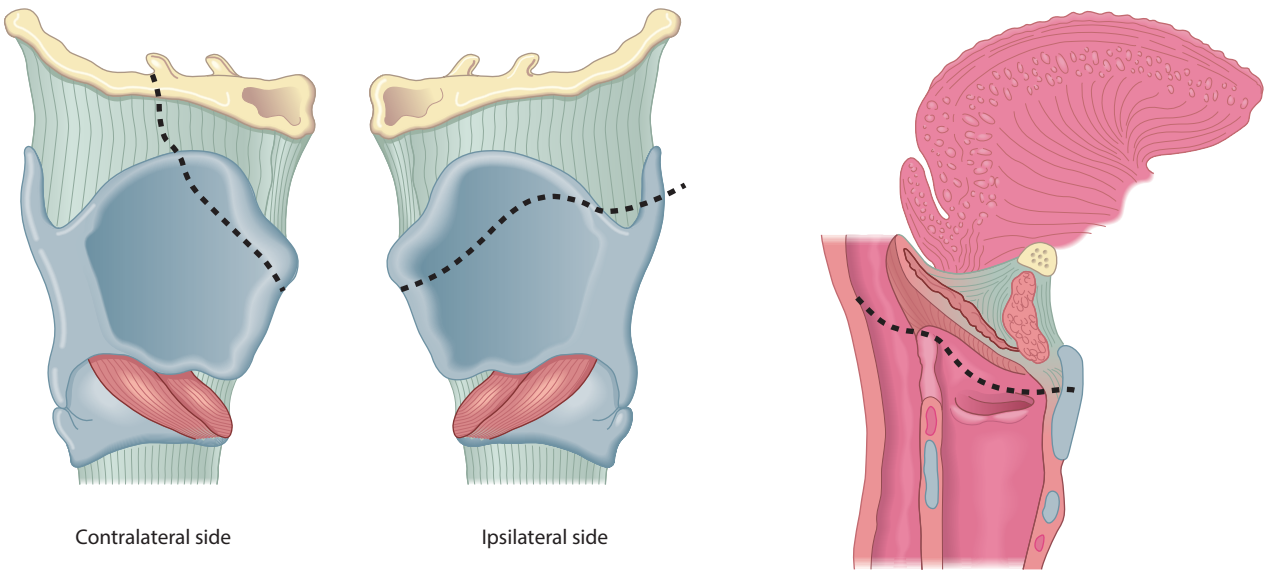

Figure 27.5 Horizontal supraglottic laryngectomy.

is transected superiorly, the ventricles inferiorly and the aryepiglottic folds laterally. Closure is by approximating the base of tongue to the lower half of the thyroid cartilage and closing the posterior false cord mucosa to the medial pyriform sinus mucosa. A temporary tracheostomy is required. Bilateral selective neck dissection is carried out at the same time, for the high rate of (contra) lateral neck metastasis from supraglottic cancers. In this procedure it is important to identify and preserve the internal and external branches of the superior laryngeal nerve. The tongue base sutures are placed in the midline and 1 cm off the midline to avoid damage to the hypoglossal nerves and lingual arteries.

Extended vertical hemilaryngectomy and reconstruction with a neovascularized tracheal autograft

Delaere et al.[15] described this two-stage technique for extended hemilaryngectomy defects involving up to half of the cricoid cartilage. Stage 1 involves tumour resection, following which reconstruction is performed using the cranial 4 cm of the cervical trachea, which is wrapped with the fascial part of a free vascularized fasciocutaneous flap from the forearm. After 4–8 weeks, the enveloped tracheal segment acquires sufficient vascular connections between the fascial soft tissue flap and trachea to allow interruption of the intrinsic blood supply, and thus grafting of the isolated segment of the trachea to the hemilaryngeal defect. Outside of select centres,[16, 17] this technique has not found widespread use; however, favourable oncologic outcomes have been reported. Significant refinements of the procedure have been presented since its original description.

Supratracheal laryngectomy

Laccourreye et al.[18] described a modification of conventional SCPL for tumours with anterior subglottic extension by removing the cricoid ring for anterior glottic tumours, which paved the way for 'functional' supratracheal partial laryngectomies (STPL), whose current version was described in 2006 by Rizzotto et al.[19]

This is aimed at laryngeal cancers with subglottic extension: this procedure involves resection of the entire glottic and subglottic sites along with the thyroid cartilage sparing both or at least one functioning cricoarytenoid unit (i.e. half of the posterior cricoid plate, with the corresponding arytenoid and the intact inferior laryngeal nerve on the same side). Inferiorly, the limit of resection encompasses the cricoid reaching the first tracheal ring. The resultant operation can be a tracheohyoidopexy – subtotal removal of the larynx maintaining one or two cricoarytenoid units and subsequent 'pexy' of the hyoid to the first tracheal ring or tracheohyoidoepiglottopexy – resection with preservation of the suprahyoid epiglottis and maintaining one or two cricoarytenoid units, followed by suspension of the tracheal ring to the epiglottis and hyoid bone.

Succo et al.[20] have detailed the indications and technique in detail; 5-year outcomes for 142 patients are as follows: overall survival from 71% to 85% and disease-specific survival from 86% to 95% based on tumour stage. Experience with this procedure has not been forthcoming from other centres.

INDICATIONS FOR OPEN PARTIAL LARYNGECTOMY

Since most laryngeal tumours are amenable to multiple different treatment options that are equally effective, the choice of therapy is determined by patient- tumour- and physician-related factors, as summarized in **Table 27.3**. In the case of untreated early laryngeal cancers, the treatment choice is typically made between primary radiation and conservation laryngectomy. Although no randomized trials have been completed, retrospective data suggest that surgical therapy may be superior with regard to local control, larynx preservation and disease-specific survival.[8, 9] When surgical treatment of early laryngeal cancers is preferred, TLM has now largely replaced open partial laryngectomy due to its lower morbidity, better voice quality, better swallowing and lower cost. Specifically, retrospective data indicate that the improved voice outcomes after TLM are similar or superior to that after primary radiation therapy.[9] Open partial laryngectomy for untreated early laryngeal cancer is indicated in select patients in whom a strong surgical preference exists, patients that fit the criteria for open partial laryngectomy (see 'Patient factors' below) but cannot be operated by TLM due to transoral inaccessibility or lack of expertise with transoral resections. In the case of advanced laryngeal cancer, a choice exists between upfront TL, (chemo) radiation and conservation laryngectomy. Although no randomized controlled trials of primary surgery vs

TABLE 27.3 Factors impacting upon choice of treatment in laryngeal cancer

Tumour factors	• Anatomic location • Extent • Volume • N-stage • M-stage
Patient factors	• Age • Comorbidity • Pulmonary reserve • Alcohol/tobacco exposure • Other cancers • Occupation • Expectations • Social support system • Motivation • Intellect • Preference • Travel distance
Physician factors	• Availability of resources • Availability of physician • Experience/skill • Comfortability • Preferences/beliefs

chemoradiation treatment have been completed, observational data and incomplete trial data indicate that TL is superior to chemoradiation in terms of oncological outcomes, whereas functional outcome data are immature at this time.[2, 6, 7, 21, 22] In well-selected patients, oncological outcomes of partial laryngectomy in this setting are similar to that of TL, and functional outcomes are better.[9, 23–25] As the experience with TLM for advanced laryngeal cancer is relatively immature, and performed routinely only in a few expert centres around the world, a choice for conservation laryngeal surgery in these patients would entail open partial laryngectomy in most instances. In advanced laryngeal cancers, open partial laryngectomy would thus be indicated in patients that fit the criteria for open partial laryngectomy, reject TL, and are unfit for or reject chemoradiation. In the setting of radiorecurrent laryngeal cancers, TL is the standard of care used by most centres. However, retrospective evidence indicates that 30–50% of patients could be safely managed by open partial laryngectomy, using stringent selection criteria.[10, 26–28] The experience with TLM in the radiorecurrent setting is immature, as retrospective evidence suggests local control rates are significantly inferior to those obtained using open partial laryngectomy.[29] Specific criteria that guide the consideration of open partial laryngectomy are described below. Careful consideration of these factors is important to minimalize the incidence of positive surgical margins, conversion to TL, and poor functional or medical outcome after surgery.

Patient factors

Stringent patient selection is critical for successful open partial laryngectomy. Patients undergoing partial laryngectomy are at increased risk of (clinically significant) post-operative aspiration, and resultant (life-threatening) pneumonias.[11, 30] This risk is exacerbated by poor wound healing, local infection and fistula formation. Although the risk and severity of aspiration varies between different types of open partial laryngectomy, patients with poor pulmonary function such as severe COPD, asthma or restrictive lung disease are poor candidates for partial laryngectomy.[12] Pre-operative assessment of lung function is mandatory in all patients considered for open partial laryngectomy but, as a general rule of thumb, the risk of pulmonary complications is well predicted by a patient's (in)ability to walk two flights of stairs.[12] Patients suffering from chronic microvascular or immunologic diseases that may impair wound healing (e.g. transplantation patients or diabetes mellitus) are also poor candidates for open partial laryngectomy for reasons described above. In patients with previous definitive radiation therapy to the cervical region, anticipation of significantly delayed wound healing should be incorporated as a factor into the treatment consideration. However, carefully selected patients may benefit from conservation surgery provided that post-operative support is stringent. The extent of the radiation portals and the total dose received are vital pieces of information that may help predict the extent of post-operative wound healing issues. For example, patients with locally recurrent T1/T2 laryngeal SCC that have been treated with standard 70 Gy IMRT-based radiation therapy and a limited glottic radiation therapy portal are expected to be better candidates for partial laryngectomy than patients treated with accelerated radiation therapy, chemoradiation, and patients with extensive base of tongue and supraglottic laryngeal carcinomas whose radiation plans have included skull base-to-clavicle type of portals. Finally, patient non-compliance is a major contraindication for partial laryngeal surgery. Successful outcome of partial laryngectomy is influenced by adequate pre-operative counselling, management of patient/family expectations, and early involvement of the speech and swallowing pathology department. Patients must be able to understand the complexities of conservation laryngeal surgery, and must be able to understand the implications of and give consent for intra-operative conversion to TL. The post-operative course after conservation laryngectomy is long and intense, and the patient (and family) should be willing and able to play an active role in speech and swallowing rehabilitation, and be available for frequent oncologic follow-up.

Tumour factors

Tumour factors that influence the choice for partial laryngectomy are primarily related to tumour location and extent within the laryngopharyngeal complex. Histological factors do not influence the choice for partial laryngeal surgery much, and most histological subtypes of laryngeal cancer can be managed successfully by this procedure. The anatomical boundaries of successful partial laryngectomy vary per type of laryngectomy, as listed in **Table 27.4.** These criteria are general guidelines, but they are not absolute and the extent of and the indications for the operation expand as the experience of the surgeon increases.

Application of vertical hemilaryngectomy is generally limited to tumours on one side of the glottic larynx, or at least not extending beyond the anterior third of the contralateral VC. The lesion should preferably not involve more than the vocal process or antero-superior part of the ipsilateral arytenoid in order to gain sufficient margin. Subglottic extension should not be more than 5 mm posteriorly, and 10 mm anteriorly (because of sufficient margin at the cricoid cartilage), whereas cranial extension should not exceed beyond the upper limit of the lateral extension of the sinus of Morgagni. Involvement of the epiglottis is a contraindication because it increases risk for pre-epiglottic space invasion. Selected patients with fixed VCs due to paraglottic extension or arytenoid fixation may benefit from hemilaryngectomy, but involvement of the RLN as a cause of cord fixation is a contraindication for hemilaryngectomy. Cartilage invasion is a contraindication to hemilaryngectomy, although microscopic erosion may not be. Hemilaryngectomy can also be applied to highly selected hypopharyngeal tumours that originate from the medial or lateral walls of the piriform sinus with secondary laryngeal extension, provided that the piriform sinus apex is free.

TABLE 27.4 Anatomic boundaries impacting on selection of open partial laryngectomy approach

	Vertical partial laryngectomy	Supracricoid laryngectomy	Supraglottic laryngectomy
Anterior	AC or anterior one-third opposite cord	Pre-epiglottic space	5 mm margin from AC
Posterior	Ipsilateral vocal process	Inter-arythenoid region	Inter-arythenoid and post-cricoid region free
Cranial	Upper limit of sinus of Morgagni	Base of tongue	Base of tongue
Caudal	Subglottic extension < 5 mm (posterior)/ < 10 mm (anterior)	Subglottic extension < 5 mm (posterior)/ < 10 mm (anterior)	Entrance sinus of Morgagni
Medial	Tumour does not cross midline (except anterior)	NA	NA
Lateral	Ipsilateral thyroid ala	Thyroid cartilage	Thyroid cartilage
General (relative) contraindications	• Epiglottic involvement • RLN involvement • Cartilage invasion • Piriform sinus apex involvement	• Extension to pharyngeal wall, vallecula, or base of tongue • Cartilage invasion • Bilateral arythenoid involvement • Bulky pre-epiglottic space involvement	• Bilateral arythenoid involvement • Cord impairment • Cartilage invasion • Tumour > 3 cm • Piriform sinus apex involvement • Impaired tongue mobility

The basis for successful supracricoid laryngectomy is that the tumour can be removed with sufficient margin, while preservation of the cricoid cartilage and at least one functioning arytenoid will provide the basis for rehabilitation. In practice, supracricoid laryngectomy results are improved significantly when both arytenoids can be preserved and sacrifice of one arytenoid should only be attempted in highly selected patients. Limitations of supracricoid laryngectomy success include gross thyroid cartilage destruction, gross pre-epiglottic space involvement, interarytenoid, bilateral arytenoid involvement, one fixed arytenoid (indicating cricoarytenoid joint invasion), subglottic extension exceeding 5 mm posterior or 10 mm anterior, and extension to pharyngeal wall, vallecula or base of tongue.

HSPL is indicated for supraglottic tumours, within the confines of parameters described in **Table 27.4**. Contraindications include less than 5 mm margin from the anterior commissure, impaired VC mobility, interarytenoid or bilateral arytenoid involvement, cartilage invasion, impaired tongue mobility, pyriform sinus apex involvement, or lesion size greater than 3 cm. HSPL may also be applied to the treatment of highly selected patients with primary tumours of the base of the tongue, medial wall of pyriform sinus and pharyngeal wall tumours, that exhibit secondary extension to the supraglottic larynx.

In patients with tumour recurrence after radiation therapy, careful assessment of tumour dimensions is even more critical, as most radiorecurrent laryngeal tumours recur with higher T-stage disease compared to the original tumour.[9] The majority of such patients require salvage TL to circumvent tumour dimensions. But salvage partial laryngectomy is possible in approximately 30–50% of patients with radiorecurrent glottic carcinomas who do not progress on therapy or who recur within the original tumour confines.[10, 26, 27] Such patients require careful endoscopic and radiologic assessment with CT scan to exclude tumour progression beyond the original tumour confines. Zbaren et al. provided a pathologic basis for this paradigm.[31] These authors showed that recurrent tumours in pathologic salvage laryngectomy specimens often exhibited dispersion of microscopic tumour deposits far beyond the original tumour confines. This observation emphasizes the underestimation of recurrent tumour dimensions on clinical and radiological examination and explains the local failure after removal of radiorecurrent tumours despite reported negative margins. Based on these findings, we recommend intra-operative frozen section analysis to help delineate the boundaries of the recurrent tumour and the need for intra-operative conversion to TL should margins be positive. Salvage supracricoid laryngectomy with CH(E)P is an alternative for larger lesions, which can give local control rates of 83.3%.[28, 32]

Of those with supraglottic carcinoma treated with radiotherapy who fail, only 30% may still be suitable for salvage conservation surgery.[9, 10, 27, 33] For supraglottic cancers, salvage partial laryngectomy by horizontal supraglottic partial laryngectomy or supracricoid partial laryngectomy and CHP is possible if the tumour has not extended beyond the original site as assessed endoscopically and by CT imaging. However, in contrast to glottic carcinomas, supraglottic tumours after RT have usually received a significant radiation dose to the base of tongue, pharyngeal constrictors and neck. This increases poor healing and fistula complications as well as post-operative swallowing problems due to fibrosis. An exaggeration of this situation is provided by (chemo)radio-recurrent base of tongue tumours with supraglottic extension (or supraglottic tumours with base of tongue extension), in which removal of the base of tongue in conjunction with HSPL in the setting of significant post-radiation fibrosis and wound healing issues increases the risk of post-operative swallowing and aspiration problems to unacceptable levels. Poor oncologic results have also been observed in supraglottic carcinomas, especially after salvage HSPL.[9, 10, 27, 33] As a result of these factors, salvage surgery for supraglottic cancer often requires a TL.

ONCOLOGICAL OUTCOMES OF OPEN PARTIAL LARYNGECTOMY

Most laryngeal carcinomas amenable to conservation laryngeal surgery can be treated with TLM or (chemo)radiation therapy with equal efficacy. Randomized controlled trials comparing different treatment modalities have not been completed. Recently, a British and an Australian trial were closed early due to accrual issues, suggesting that randomized data to answer the question will not be available within the near future.[9] Data on the outcome of partial laryngeal surgery are available from several large retrospective studies, and can be compared to that of patients treated with (chemo)radiation or TLM. Local control and LP are the primary aim of the different treatment modalities, as disease-specific death from early laryngeal cancer is approximately 1–3%. Therefore, they are primary clinical endpoints of interest in scientific analyses of oncologic results.

A systematic review of 53 articles[33] including 5061 patients treated with open partial laryngectomy reveals that pooled local control rate at 24 months was 89.8% (95% CI: 88.3–91.2%). The pooled larynx preservation rate (assessed in 3171 patients) was 90.9% (95% CI: 8.8–92.7%). These overall data compare favourably with (chemo)radiation results and suggest that partial laryngeal surgery should be offered as an alternative treatment option to patients who qualify for organ preservation treatment.[9, 33] However, the outcome of laryngeal treatment is heavily influenced by disease stage, and anatomic location within the larynx and should therefore be analyzed within the context of these factors.

Glottic carcinomas

Treatment with open partial laryngectomy gives local control and LP rates in T1 SCC between 92% and 100%.[9] In T2 tumours, local control is between 69% and 93%, but LP after salvage surgery still reaches 93%.[9] TLM in T1 tumours achieves 85–95% local control rates and 95–99% LP after 5 years, whereas in T2 tumours, 65–85% local control rates and 83–96% LP after 5 years can be obtained.[9] Retrospective data suggest that the oncologic efficacy of primary radiation treatment may be similar to surgery, with local control between 85% and 93% and LP 89–96% for T1 tumours, and local control 57–80% and LP 73–82% for T2 laryngeal SCC.[9] Adversaries of radiation treatment further argue that the RT efficacy for early laryngeal cancers may be significantly overestimated, due to the fact that up to 30% of patients that qualify for and are included in primary RT treatment protocols, may have been cured by their pre-RT biopsy already.[9]

Factors that influence outcome in the early laryngeal cancer setting include anterior commissure (AC) involvement and VC mobility impairment.[9] Although tumours with AC involvement are unlikely to harbour a more aggressive clinical course, AC involvement does complicate surgery, which may account for decreased survival rates.[9] Steiner et al. suggested that local control may be 10–15% worse when AC is involved, and LP may be 5% worse overall.[34, 35] Their results were confirmed in a follow-up study of 444 patients.[34, 35] Laccourreye et al. reported 23% local failure after vertical partial laryngectomy in 416 cases of AC involvement.[36] When SCPL-CHEP was applied, local failure was improved to 98%, but most patients had also received an induction chemotherapy regimen in their series.[37, 38] No differences were found when open vs TLM approaches were compared in cases with AC involvement.[9] On the other hand, Peretti did not find differences in local control with or without AC involvement.[39] A literature review by Herranz suggests that all three treatment options have similar results when involvement of the AC is present.[9, 40]

Impairment of VC mobility is also an adverse predictor of outcome in early laryngeal SCC. T2 tumours with impaired VC mobility exhibit reduced local control and LP that is more akin to that of T3 carcinomas with VC fixation.[9] Local control rates in cases with true vocal cord (TVC) impairment or fixation treated with open partial hemilaryngectomy ranges between 52% and 76%.[9] However, local control and LP can be improved to 95% in this patient population with the application of supracricoid laryngectomy as per French data, but the majority of these patients received induction chemotherapy and many received post-operative RTx.[9] Studies using TLM have shown that local control was 74% in T2b, and 68% for T3 tumours, whereas LP was 85% in both groups.[9] Ultimately, 5-year local control was 87%, and disease specific survival (DSS) was 62% in both groups. Three large case series with more than 100 patients each of T2N0 disease, with organ preservation rates of 84–96%, are observed for T2N0 tumours.[41–43]

Limited literature data exist on TLM for more advanced laryngeal carcinomas. Recently, Steiner et al. published on 226 cases of T3 SCC showing a local control and LP rate of 71.4% and 87% respectively.[23] Radiation therapy reaches local control in TVC impairment between 60% and 76%, and LP is 70–80%.[9] The collective data suggest that the oncologic efficacy of open partial laryngectomy is similar to that of TLM, but superior to primary RTx.

Supraglottic carcinomas

In the case of supraglottic carcinomas, high local control rates are obtained for selected early tumours treated with open partial laryngectomy.[44] HSPL has local control of 90–100% for T1 tumours, and 80–97% for T2 tumours.[9] For T3 SCC, local control rates are 71–94%.[9] In T4 lesions, local failure is approximately 67%.[9] Therefore, HSPL should be considered with extreme caution in T3 and T4 lesions. Literature data suggest that application of supracricoid laryngectomy with CHP may improve these figures slightly,[9] where local control can be as high as 96% of patients, at the expense of significant aspiration. The reason for these favourable results is the *en bloc* resection of bilateral paraglottic spaces, pre-epiglottic space and thyroid cartilage. However, it should be noted that a majority of patients in these studies received induction chemotherapy before supracricoid laryngectomy, which may influence the data. Several small studies describe the results of TLM for supraglottic tumours showing similar results to the open approach.[9] Radiotherapy results show that T1 supraglottic tumours have local control of 75–100%, and

T2 have local control of 62–83%.[9] T3 supraglottic carcinomas are rarely treated with RT alone, following the demonstration of improved local control with the addition of concurrent chemotherapy in the 91–11 trial.[5] Comparable to the data on glottic tumours, these retrospective data suggest that open partial laryngectomy as primary treatment for supraglottic cancers achieves equal success rates compared to TLM, but is superior to primary RT.

Radiorecurrent carcinomas

Radiorecurrent tumours treated with partial laryngectomy are virtually all T1 and T2 tumours, as more advanced lesions typically require TL. A recent meta-analysis of the English language literature reported a pooled local control rate of 86.9% (95% CI: 84–89.5%), identified from 26 articles including 560 patients undergoing open partial laryngectomy for radiorecurrent disease.[10] The pooled mean larynx preservation rate derived from analysis of 502 patients was 83.9% (95% CI: 80.7–87%). When excluding patients with supraglottic tumours, the pooled salvage laryngectomy rate was 9.2% (95% CI: 7.4–11.1%) in 253 patients, and the pooled laryngectomy rate for aspiration was 4.4% (95% CI: 2.2–7.4%) in 224 patients. For 159 T1 ($n=124$) and T2 ($n=35$) tumours treated with vertical hemilaryngectomy the pooled local control rate was 84.4% (95% CI: 84.4–84.4%), and the mean LP rate was 85%. Virtually all total laryngectomies were performed for oncologic salvage. One hundred and forty-nine patients treated with supracricoid laryngectomy had pooled local control 93.9% (95% CI: 91.8–95.8%), and mean LP rate was 83.1%; 2.6% of patients required a TL for aspiration. Disease-free survival was similar between these treatments, approximately 80–85%. Few studies have analyzed the efficacy of supraglottic laryngectomy for radio-recurrent laryngeal SCC. These studies suggest that the local control rates are significantly lower than observed for the other procedures.[10, 27, 32] The experience with TLM for radiorecurrent disease has thus far been small, and insufficient for adequate comparison. Altogether, the literature suggests that approximately 30–50% of patients with radiorecurrent SCC may benefit from salvage open partial laryngectomy, with control rates equal to TL in these patients.

COMPLICATIONS AND FUNCTIONAL OUTCOMES OF OPEN PARTIAL LARYNGECTOMY

Post-operative complications

Complications after conservation laryngeal surgery can be categorized into local (wound infection, dehiscence, fistula, chyle leak), swallowing (dysphagia, stricture), airway (aspiration pneumonia, laryngeal stenosis, laryngeal oedema, granuloma formation, surgical emphysema, perichondritis, CH(E)P breakdown) and systemic (cardiac, pulmonary, renal, infectious, metabolic). The rate of overall complications after partial laryngectomy is approximately 20%.[11, 29, 45, 46] Of these, local complications are most common, and occur between 8% and 11%. The fistula rate after partial laryngectomy is between 2.5 and 4%. Prior RT is the most important predictor of local complications including fistula formation. Local complications after salvage partial laryngectomy have been described to occur in 24% of patients, and fistula formation after salvage partial laryngectomy occurs in approximately 14% of cases. Ganly et al. found that prior RT was associated with a 13-fold increase in local complications and fistula formation after partial laryngectomy, an increase that was statistically significant.[45] Several authors have suggested that the type of partial laryngeal surgery is a predictor of complications, with more extensive laryngeal surgery such as supracricoid laryngectomy associated with increased complication rates in univariate statistical analysis.[11, 29, 45, 46] It is currently unclear whether type and extent of open partial laryngeal surgery is an independent predictor of the complication rate in multivariate analysis, but it is clear that partial laryngeal surgery using TLM is associated with significantly lower rate of complications due to less extensive dissection, and absence of need for tracheostomy and percutaneous feeding tube in most patients.[9]

Functional outcomes

Functional outcome of partial laryngeal surgery is influenced by pre-operative factors (patient age, comorbidity, pulmonary status, tumour stage and pre-operative radiation), intra-operative factors (location and extent of resection) and post-operative factors (patency of airway, patency and mobility neoglottic valve, patency and mobility of (oro) pharynx, laryngopharyngeal sensation and the position of the laryngeal remnant in relation to the base of the tongue). Although functional recovery after partial laryngectomy can be qualified in several ways, decannulation rate, time to permanent decannulation, permanent gastrostomy rate, and need for TL for intractable aspiration (functional laryngectomy) are some of the more objective parameters to describe it.[22] Also, these parameters are unequivocal, objective, and allow for reliable comparison with other treatment modalities. Parameters to objectify voice outcomes are less well defined, although this is obviously also a critical outcome parameter after partial laryngectomy.

A recent meta-analysis of primary open partial laryngectomy outcomes[33] found that the pooled decannulation rate among 3955 patients derived from analysis of 42 studies was 96.3% (95% CI: 94.9–97.6%). The permanent gastrostomy rate among 2000 patients derived from 20 studies was 2% (95% CI: 0.9–3.6%). The functional laryngectomy rate was 1.7%. Although the authors excluded salvage partial laryngectomy patients, they did not stratify their data by type of partial laryngectomy. Functional outcome data from individual series demonstrate that tracheostomy and nasogastric feeding tubes can generally be removed within 1–2 weeks from vertical partial laryngectomy, and (temporary) gastrostomy tubes are generally not necessary after this type of procedure.[38, 45, 47, 48] Voice outcome data after VPL have not been reliably assessed. In the case of HSPL and SCPL, post-operative aspiration and airway issues are

generally more severe, and temporary but clinically significant aspiration (Pearson grade 2–3) has been described in 10–20% of patients, while aspiration pneumonia has been reported in 10% of patients after SCPL.[11, 29, 46, 49, 50] Time to decannulation and nasogastric feeding tube removal approaches 1–2 months in most patients, but most patients will require 6–12 months to approach their normal eating habits. Prophylactic gastrostomy tube placement is recommended in a proportion of high-risk patients after SCPL and HSPL. Predictors of clinically significant aspiration include arytenoid sacrifice, advanced age, radiation therapy and CHP reconstruction. However, the rates of permanent gastrostomy, tracheotomy and functional laryngectomy are below 5% in experienced hands and well-selected patient populations. SCPL causes an inevitable change in voice quality, which can adversely affect the QOL, especially in female patients.[51, 52] The functional outcome after salvage partial laryngectomy has been described in a recent meta-analysis.[10] The pooled mean decannulation rate among 315 patients was 95.1% (95% CI: 92.6–97.2%). Eleven studies reported a mean or median time from surgery to decannulation that ranged from 7–31 days. Other functional outcome data could not be reliably extracted from the included studies. In comparison to open partial laryngectomy, the functional outcomes of TLM partial laryngectomy are significantly better.[9] This can be attributed to avoidance of tracheotomy, preservation of hyoid bone and supra/infrahyoid muscles and pharyngeal muscles, and preservation of the extralaryngeal portions of the SLNs. Functional outcomes after RT and chemo-RT are not well described. Recently, publication of the long-term data of the RTOG 91–11 trial[7] demonstrated that 43% of patients had severe late complications, including an 18% rate of pharyngeal dysfunction (significant swallowing problems in 17–25% in concurrent CRTx group, and 13% of the induction chemotherapy and radiation alone groups), and 25% rate of laryngeal dysfunction. In addition, a 7% unexplained death rate was observed in the chemoradiation treatment arm, in addition to a high rate of complications associated with salvage TL after chemoradiation treatment. These data suggest that partial laryngeal surgery is superior to (chemo)radiation in terms of functional adequacy after treatment.

CONCLUSION

Organ preservation management for laryngeal cancer is a desirable treatment avenue. Although no phase III trials have been completed, our best available evidence suggests that conservation laryngeal surgery is a safe approach in selected patients, and is superior to primary (chemo) radiation in these patients in terms of oncologic efficacy and functional outcome. Although TLM is the preferred approach for conservation laryngectomy patients due to its less invasive nature and lower rate of complications, a specific indication for open partial laryngectomy still exists in selected patients who qualify for conservation laryngeal surgery. These include transoral inaccessibility of the tumour, salvage after radiation treatment, and lack of expertise with TLM. For these specific indications, the skill of open partial laryngectomy is important and should remain in the armamentarium of the head and neck surgeon.

KEY POINTS

- Total laryngectomy offers the best chance for cure across all laryngeal cancer types and stages but has the poorest functional outcome.
- Conservative organ-preservation laryngeal cancer treatments include (chemo)radiation and conservation surgery including transoral laser-assisted microsurgery (TLM) and open conservation laryngeal surgery.
- Conservation laryngeal surgery offers better oncologic and (long-term) functional outcomes than (chemo)radiation in properly selected patients.
- TLM offers similar oncologic outcomes but has decreased complication rates and superior functional outcomes to open conservation laryngeal surgery.
- The spectrum of open conservation laryngeal surgery encompasses several different procedures categorized by their anatomic focus (glottis or supraglottic disease), anatomic extent and surgical orientation (horizontal or vertical).
- Indications for open conservation laryngeal surgery are guided by well-defined patient, tumour and physician factors.
- Functional pulmonary reserve is the most common limiting factor for successful conservation laryngeal surgery, as most laryngeal cancer patients feature significant degrees of COPD.
- The surgical goals of open conservation include attainment of negative margins and optimization of functional outcome through preservation of (a) structurally and functionally adequate airway, alimentary tract and neuromuscular coordination.
- Oncologic and functional outcomes of open conservation laryngeal surgery support its application in properly selected (chemo)radiation-naïve and (chemo)radio-recurrent laryngeal cancers.

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CHAPTER 28

MEASURES OF TREATMENT OUTCOMES

Helen Cocks, Raghav C. Dwivedi and Aoife M.I. Waters

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SEARCH STRATEGY

A search strategy, developed for PubMed, combining MeSH terms for head and neck cancer, patient reported outcomes, treatment outcomes, health-related quality of life, voice, speech and swallowing was used.

INTRODUCTION

Outcome assessment constitutes an integral part of patient management. Modern healthcare systems demand robust outcome measures, which should be disease specific and reflect the concerns of the patient. Their measurement is compounded by the fact that patients, carers and healthy 'observers' have different opinions as to what constitutes the most favourable outcome.[1]

Historically, the success of head and neck cancer (HNC) treatment and treatment in general has often been described in terms of survival rates and disease control. However, since patients seek treatment on the basis of their symptoms rather than the underlying diagnoses, one can argue that survival alone cannot be considered truly reflective of the outcomes as it omits measures of function. This can often lead to a paradox of excellent results in medical terms, but unsatisfactory/unacceptable outcomes from the patient's perspective.

Outcomes can therefore be divided into survival outcomes and functional outcomes, which ultimately determine the quality of life (QOL) of a patient. QOL, which is another important concept in the arena of outcomes is discussed at greater length in Chapter 20, Quality of life and survivorship in head and neck cancer.

SURVIVAL OUTCOMES

Undoubtedly, survival remains the cornerstone of outcome assessment for HNC. Analysis of survival has the advantage that there can only be two categories: alive or dead and this outcome cannot be misrepresented. However, this measure is insensitive in diseases with low mortality and there are many inaccuracies in recording the cause of death. Most importantly it disregards functional outcomes and QOL.

'Time-to-event' analysis

Survival analysis is based on scientific fundamentals and techniques of statistics, which analyze 'time to event' and can be used for many outcomes apart from death (**Box 28.1**).

Two key facts should be recognized in time-to-event analyses. The distribution of the data is mostly non-parametric and thus appropriate statistical techniques should be used for analyses. Some patients do not experience the event either because they are lost to follow-up or they were still alive at the end of the study. These patients represent censored events or censored observations.[2]

The Kaplan–Meier survival curve is the most common means of expressing survival and other such binary events in a study group.[3] It is used to estimate survival rates and hazards from such incomplete data assuming that those censored subjects have the same prospect of survival as uncensored subjects. The median survival time is the time at which the cumulative survival is equal to 0.5. The log rank test provides methods for comparing two or more survival curves, but is only appropriate where relative mortality does not change over time (proportional hazards assumption).

BOX 28.1 Survival analysis

PARAMETERS OF SURVIVAL

- **Overall survival (OS)** – The length of time from either the date of diagnosis or the start of treatment for a disease, such as cancer, that patients diagnosed with the disease are still alive.
- **Disease-free survival (DFS)** – The length of time after primary treatment for a cancer ends that the patient survives without any signs or symptoms of that cancer. Also called *relapse-free survival.*
- **Progression-free survival (PFS)** – the length of time that a patient lives with the cancer, but it does not get worse.
- **Disease-specific survival rate** – The percentage of people in a study or treatment group who have not died from a specific disease in a defined period of time. The time period usually begins at the time of diagnosis or at the start of treatment and ends at the time of death. Patients who died from causes other than the disease being studied are not counted in this measurement.
- **Median survival (MS)** – The length of time from either the date of diagnosis or the start of treatment for a disease, such as cancer, that half of the patients in a group of patients diagnosed with the disease are still alive. Also called *median overall survival.*

ANALYSIS OF SURVIVAL

- **Kaplan-Meier survival curve** – Most common method used to estimate survival rates and hazards assumes with incomplete data, as seen with survival, that those censored subjects have the same prospect of survival as uncensored subjects.
- **Log rank analysis** provides methods for comparing two or more survival curves, but is only appropriate where relative mortality does not change over time (proportional hazards assumption).

FUNCTIONAL OUTCOMES

Functional outcomes define anatomical and physiological impairment, disability and handicap that occur secondary to a disease process or the treatments for these and can, ultimately result in a poor QOL.[4]

Functioning, disability and health

The World Health Organisation has classified functioning, disability and health based on the ICF (International Classification of Functioning, Disability and Health). This is a classification looking at the loss/limitation of function. Disability underscores the consequences arising from this loss of function and health, reflects the disadvantages experienced by the patients as a consequence of the impaired functions and disabilities and highlights the interaction with and adaptation to their environment and in relation to their peer group and society in general.

Treatment for HNC is likely to affect some of the most basic human functions – verbal communication, social interaction, eating and breathing. It is easy to see how speech and swallowing can be affected in patients undergoing resection for large oral cavity or oropharyngeal lesions and in the most extreme case of the laryngectomy. However, with the use of concurrent chemoradiotherapy showing approximately the same long-term survival, much emphasis has been placed on organ preservation.[6] Therefore, the clinical trade-off is no longer the length of life, but functional outcome and QOL. It should be noted that anatomical preservation does not guarantee function and patients experience several debilitating side effects with organ sparing treatment paradigms, where voice quality is reduced and swallowing problems are common due to the stiffening of tissues in the pharynx and upper oesophagus. A disease-specific QOL survey covering five domains (speech, eating, aesthetics, pain/discomfort and social/role functioning) demonstrated that speech and eating had the most impact on well-being.[7] It is estimated that as high as 35–75% HNC patients suffer from speech and swallowing problems after such treatment.[8]

Which measures to choose?

Currently, there are no outcome reporting standards for clinical practice or trials in HNC. The World Health Organisation (WHO) recommended as early as 1981 that as a minimum standard, oncology clinical trials should measure tumour and metastasis response, duration of response and adverse effects.[9] Furthermore, the publication of the International Classification of Functioning, Disability and Health for head and neck cancer (ICF HNC) provided a framework for classifying health and health-related domains for measuring health and disability at both individual and population levels.[10] Whilst survival outcomes are critical, health-related QOL and functional outcomes are given less consideration and measured in a far less consistent or rigorous manner.[11] As survival rates improve, however, survivorship issues become increasingly relevant.[12–16]

In the majority of cases, clinicians and trialists make decisions about which outcomes of treatment should be measured. As a result, the data collected and measured may not reflect outcomes of importance to patients, and the lack of standardization makes comparison of outcomes difficult, if not impossible. Small numbers, tumour heterogeneity and incidence of post-treatment functional deficits provide particular challenges when choosing outcomes for patients with SCCHN. For systematic reviewers and guideline developers, disparate outcome measurement precludes the synthesis of individual trial data in

meta-analyses, and much research thus fails to contribute to the evidence base.[17]

Core Outcome Sets (COS) have been proposed by the COMET initiative to ensure that outcomes important to both patients and clinicians are measured consistently, thus facilitating the synthesis and/or comparison of outcomes.[18] A COS is a minimum outcome reporting standard for use primarily in clinical trials, but also in audit and clinical practice that is specific to a clinical condition or area of healthcare.[19] The use of a COS does not preclude the measurement of other outcomes, rather it ensures that 'core' outcomes are measured consistently, allowing for the collection of more rigorous outcomes data.[18]

A COS has been developed for clinical trials in oropharyngeal squamous cell carcinoma (OPSCC) and is in the pre-publication phase.[20]

Once the outcomes to be included in a COS have been chosen, research to establish the best instruments for measuring the outcome must be undertaken. The **C**onsensus-based **S**tandards for the selection of Health Measurement Instruments (COSMIN) initiative make recommendations about '*how*' the identified outcomes should be measured.[21] The COSMIN checklist can be used to appraise the methodological quality of studies on measurement properties and to check whether all important design aspects and statistical methods have been clearly reported.[21]

Multiple outcome measurement tools abound but there appears to be no consensus among clinicians regarding what to use and when. Choosing the most appropriate outcome measure is essential to evaluate both the effectiveness and efficacy of any treatment and rehabilitation. Outcome measurements may be subjective or objective, patient rated or clinician rated, and may take the form of questionnaire or instrument-based assessment. Ideally, specific, validated tools should be chosen.[22]

Increasingly, patient reported outcomes (PROs) are used. They measure how a patient feels or functions and are collected directly from the patient without interpretation by a clinician. They are often collected using measurement tools (PROMs) that assess the patient's view of their symptoms, functional status or QOL.[23] One could argue whether objective or subjective measures are more valuable, indeed there is poor correlation between objective and subjective measures of xerostomia in this patient population.[24]

MEASURES OF TREATMENT TOXICITY

A variety of scoring systems are used to measure toxicity, and the time points at which these are measured vary. Both acute and late toxicities are encompassed by the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Effects.[22] Version 3.0 largely superseded the Late Effects of Normal Tissue (LENT SOMA) and Radiation Therapy Oncology Group- European Organisation for the Research and Treatment of Cancer (RTOG-EORTC) scales, and was updated to version 4.0, June 2010.[25] Late effects are generally accepted as those occurring 6 months beyond the end of treatment.

Xerostomia

Xerostomia is an acute and late adverse effect of radiotherapy to the head and neck, and is most often graded according to the toxicity criteria described above or as part of HR-QOL tools. Patients consider dry mouth to be a top priority after treatment for HNC. Eisbruch et al[26] implemented an 8-item self-reported xerostomia-specific questionnaire (XQ) in patients receiving parotid sparing IMRT. The XQ was found to be reliable and valid in measuring patient-reported xerostomia.

Shoulder dysfunction

Like xerostomia, shoulder dysfunction is most often measured as part of HR-QOL measures. No specific PROM exists.[26]

Voice or speech?

Voice and speech represent different ends of the same spectrum, explained by the source-filter theory. The larynx serves as the source of phonation thereby producing voice, while the vocal tract (oral cavity, oropharynx, nasopharynx, nasal cavity and paranasal sinuses) acts as a filter thereby altering the voice and shaping speech. Speech is the final outcome of voiced sound, which is characterized by resonance, nasality and articulation.[27] Cancers or treatments involving these sites will affect speech and not the voice.

MEASURES OF VOICE OUTCOMES

Voice is predominantly affected by laryngeal cancers or treatments affecting the larynx, directly or indirectly. There are numerous tools used for the evaluation of voice throughout the world (**Box 28.2**), but there exists no widely accepted voice outcome measure. Some of the commonly used tools are described in **Box 28.2.**

Questionnaire-based measures

Voice Handicap Index Voice Handicap Index (VHI)[28] is a validated, self-assessment scale that measures patient perception of the impact of dysphonia on various aspects of routine living. It is one of the most widely used voice questionnaires. It consists of 30 statements on voice-related aspects in daily life each with a scores ranging from 0 to 4. The maximum score is 120, values above 60 indicate a severe disability, those between 40 and 60 moderate disability and less than 40 mild or no disability. The questions are divided into three subscales or domains: physical, functional and emotional, with ten questions in each.

It has been used extensively as an outcome assessment tool in laryngeal cancer in both patients with a laryngeal and alaryngeal voice. VHI-based comparative voice outcomes following laryngeal cancers treated with either

BOX 28.2 Tools available for the assessment of outcome of voice

QUESTIONNAIRE BASED MEASURES

- Voice Handicap Index (VHI)[28]
- Voice Symptom Scale (VoiSS)[29]
- Voice Activity and Participation Profile (VAPP)[30]
- Voice Prosthesis Questionnaire[31]
- Vocal Handicap Index-10[32]
- Vocal Performance Questionnaire (VPQ)[33]

PERCEPTUAL MEASURES

- GRBAS rating scheme[34]
- Perceptual evaluation of alaryngeal speech

INSTRUMENT-BASED MEASURES

- Stroboscopy[35]
- Acoustic analysis of voice using inverse filtering and linear predictive coding[36]
- Electroglottographic (EGG)[37]
- Electromyographic analysis[38]

surgery or radiotherapy,[39] transoral laser excision of early laryngeal cancers,[40] endoscopic laser versus open resection,[41] supracricoid partial laryngectomy,[42, 43] alaryngeal voice[44] and chemoradiotherapy[45] and have all been published in the literature.

Voice Symptom Scale The Voice Symptom Scale (VoiSS)[29] is one of the most rigorously evaluated voice questionnaires. It contains 30-items to assess three aspects of voice: impairment, emotional and physical symptoms. The VoiSS is becoming more widely used in HNC patients to assess voice.[46, 48] In a study looking at patients with early glottic cancer treated by endoscopic resection or radiotherapy similar results were produced for the VHI, VoiSS or VPQ. The exception was the emotional subscale of the VoiSS, which gave better results for those treated with radiotherapy and in addition reflected the concurrent pharyngeal symptoms.[47]

Voice Activity and Participation Profile Voice Activity and Participation Profile (VAPP)[30] is a 28-item questionnaire validated in number of languages. It consists of five sections: self-perception of voice, effect on job, effect on daily communication, effect on social communication and effect on emotion. Each item uses a visual analogue scale 10 cm long ranging from not affected to always affected.

Voice Prosthesis Questionnaire The Voice Prosthesis Questionnaire[31] has been locally validated and looks specifically at the surgically voice-restored laryngectomee. It is a self-administered 45-point questionnaire and has sections relating to speech, leakage, valve changing, maintenance, QOL, humidification and hand-free issues.

Short-form self-assessment questionnaires

Long questionnaires can be time consuming to complete and the score may provide a degree of redundant information. They are useful research tools, but in the clinical setting concise, clinically useful self-report questionnaires are of more use. Two short-form, rigorously evaluated, voice-related scales are available, the Vocal Handicap Index-10 item questionnaire (VHI-10) and the Vocal Performance Questionnaire (VPQ).

Vocal Handicap Index-10 item questionnaire Item analysis of VHI by patients with voice disorders and controls identified the 10 most robust VHI items resulting in the creation of the Vocal Handicap Index-10 item questionnaire (VHI-10).[32] Similar to the VHI, a five-point item scale is used with scores ranging from 0 to 4, resulting in a total score of between 0 and 40.

Vocal Performance Questionnaire The VPQ[33] is a 12-item questionnaire which examines the physical symptoms and socio-economic impact of the voice disorder. The patient selects a statement that best answers each question. The statements are graded in terms of severity of vocal performance. A numerical score of 1–5 is assigned to each answer and these are summed to provide an overall score of vocal severity – maximum score 60 and minimum score 12.

These two short-form voice related scales (VPQ and VHI-10) use a single total score and correlate highly with one another.[48]

Perceptual measures

GRBAS The GRBAS rating scheme[34] is considered as a practical minimum standard for the perceptual rating of voice.[49, 50] It consists of five domains: grade (representing overall voice quality), roughness (which looks at fluctuations in F0, indicative of vocal edge abnormalities), breathiness (which assesses air escape), asthenia (a general decrease in power of or weakness of the voice) and strain (which assesses hyperfunctionality). All are assessments of laryngeal function.

Assessment is made on a recording of a voice reading an established phonetically balanced passage, such as the 'rainbow passage' or on current conversational speech. Each aspect of the GRBAS scale is given a score of 0–3, where 0 is normal, 1 shows slight deviance, 2 moderate deviance and 3 severe deviance. This scale has been shown to be reliable across all parameters except strain.[51]

The GRBAS scale has been used in the assessment of voice in the HNC population, including partial laryngeal surgery, in the comparison of radiotherapy and laser excision in the treatment of early glottic lesions. It has also been used as a tool to assess alaryngeal speech[52, 53] Interestingly little correlation has been shown between self-assessment using VHI and clinician-rated GRBAS assessment with severely dysphonic supracriciod laryngectomy patients scoring mean values of 29.9 on VHI.[42]

Perceptual evaluation of alaryngeal speech Although attempts have been made to develop a scale for perceptual evaluation of alaryngeal speech, a reliable, reproducible perceptual rating system does not seem to exist for the laryngectomee. Van As et al[54] report the use of a semantic

bipolar seven-point scale (e.g. ugly–beautiful, deviant–normal, low–high), for both untrained and trained raters. Eadie and Doyle report the use of direct magnitude estimation (continuous) and equally appearing interval scales for the auditory perceptual rating of naturalness, severity, acceptability and pleasantness of tracheoesophageal voice.[55–57] Hurren and Miller report no current evidence to support the use of acoustic instrumental measures in terms of validity. They show preliminary data support for the validity of a new tracheoesophageal voice auditory-perceptual tool the SToPS, for professional and native raters.[58]

Instrument-based measures

A number of instrument-based measurements of voice can be used to diagnose and evaluate the nature and severity of dysphonia. Only a few are useful in measuring changes in voice quality with time. Most have little use in the assessment of outcome in the HNC patient. The more common and potentially useful measures are mentioned in **Box 28.2.**

Acoustic measures of voice Acoustic analysis[36] is widely used in testing vocal function because it is objective and reproducible, as long as the same equipment is used on each occasion. A voice sample is recorded on to digital audiotape (DAT) and acoustic measurements of the voice/speech signal can be made such as maximal phonation time (MPT), frequency, fundamental frequency (the lowest tone in the harmonic), Jitter 1st (the pitch perturbation or frequency variability in percentage), Jitter 2nd (the average of the differences between successive differences in the frequencies of successive periods in percentage) and Shimmer (the amplitude perturbation or intensity variability in dB from the acoustic waveform).

The main use of acoustic measurements in HNC patients has been to compare outcomes of treatments for early glottic tumours,[59, 60] in the assessment of voice after supracricoid laryngectomy[61] and in the assessment of speech therapy following treatment for such lesions.[62] These measurements have also been assessed in the laryngectomee in which the voice is often aperiodic, and makes the assessment of these acoustic measures even more challenging.[63] A detailed treatment of acoustic measures can be found in Chapter 62, Evaluation of the voice.

MEASURES OF SPEECH OUTCOMES

Normal speech is clearly intelligible, well articulated and has adequate nasal components due to oro-nasal separation.[64] Tumours or treatments involving the vocal tract can alter speech.[65] Speech as a function is generally ignored and poorly investigated in HNC patients.[27] Measures currently in use for assessment of speech outcomes are summarized in **Box 28.3.**

Questionnaire evaluation of speech

Speech Handicap Index (SHI) The speech handicap index (SHI) was developed in 2008 by Rinkel et al[67] Recently an English version was validated.[27] It consists of 30 questions to evaluate the patient's speech and speech-related psycho-social functions. Scoring of SHI is based on a Likert five-point scale with response categories as never (0); almost never (1); sometimes (2); almost always (3) and always (4). Total SHI score is summed and higher scores indicate worse speech-related problems. In addition, there is a global question which rates the patient's overall speech quality, this has four responses: excellent; good; average and bad which are scored as 0, 30, 70 and 100. Higher scores again indicate a greater speech problem.

Perceptual evaluation of speech

This is considered gold standard for speech evaluation and involves speech rated by professionals for different speech parameters.

The London Speech Evaluation 'LSE' scale This has recently been developed and validated for use in HNC patients.[64] It evaluates five speech parameters, intelligibility, articulation, rate, nasality and asthenia and overall grade of speech impairment. Scoring of the instrument is based on a Likert four-point scale ranging from 0 to 3. Higher scores indicate greater impairment.

Assessment of Intelligibility of Dysarthric Speech The Assessment of Intelligibility of Dysarthric Speech (ASSIDS)[66] is used by speech and language therapists and contains assessment of intelligibility of speech. It requires a recording of either 50 single words or sentences of 5–15 words selected at random. Each sample is judged by a pool of scorers (one scorer can be used if improvement is being sought in an individual patient). The recording is listened to and transcribed by the scorer and an intelligibility score given as a percentage of responses that were correct. In addition to percentage intelligibility, scores can be calculated for speaking rate, rate of (un)intelligible speech and a communication efficiency ratio. These calculations are based on a healthy person speaking a 220-word paragraph at a rate of 190 words per minute.

Instrument based measures

Acoustic evaluation of speech Acoustic evaluation of speech measures acoustic parameters like fundamental

BOX 28.3 Tools available for the assessment of outcome of speech

QUESTIONNAIRE BASED MEASURES

- Speech Handicap Index (SHI)[27, 66]

PERCEPTUAL MEASURES

- The London Speech Evaluation 'LSE' scale[64]

INSTRUMENT BASED MEASURES

- Assessment of Intelligibility of Dysarthric Speech (ASSIDS)[66]
- Acoustic analysis of speech signal using linear predictive coding[36]

frequency (F0) and formant frequencies. These are the natural resonance frequency of vocal tract for certain sounds and vowels in particular can be identified by their formants. There are several formants but only the first (F1), second (F2) and third (F3) formant frequencies are of use in speech evaluation of HNC. F1 and F2 are related to tongue position and F3 to size of oral cavity. Formants are extracted through linear predictive coding (LPC). Formant frequencies objectively measure approximation between various portions of the oral cavity and the oropharynx.[68] Currently, acoustic analysis of speech is still in its infancy and is predominantly used as a research tool.

MEASURES OF SWALLOWING OUTCOMES

Dysphagia assessment requires a multimodality approach (**Box 28.4**) and falls broadly into two categories: those that assess the severity of the swallowing disorder and those that try to establish its cause.

Causation generally relate to the biomechanics of the altered swallow mechanism, whether sensory or motor. The choice of examination depends largely on the clinical questions to be answered and the presentation of the patient.

Questionnaire evaluation of swallowing

Sydney Swallow Questionnaire (SSQ) This tool is for evaluation particularly of oral and-pharyngeal dysphagia;[73] it has been recently validated for use in the HNC patients.[74] It consists of 17 well-structured questions for the assessment and quantification of patient reported difficulties with swallowing.[73] It uses a visual analogue scale; the total score is calculated and ranges from 0 to 1700 with higher scores indicating a more severe swallowing impairment.

SWAL-QoL and SWAL-CARE SWAL-QoL[75] is a validated swallow-specific QOL questionnaire to assess oropharyngeal dysphagia. It consists of 44 questions grouped in several subsections to evaluate 10 different QOL domains related to swallowing, based on a 5-point scale. It remains the most comprehensive assessment of swallow performance to date. The SWAL-CARE is a 15-item tool relating to quality of care and patient satisfaction.

MD Anderson Dysphagia Inventory (MDADI) The MDADI[76] is one of the most commonly used swallowing questionnaires for HNC patients. It is a self-administered 20-item questionnaire divided into four domains (Global, Emotional, Physical and Functional). The Emotional, Physical and Functional domains consist of 6, 8 and 5 questions respectively, which are scored on a scale of 1 to 5. All (but one) questions are summed, and a mean score is then calculated. This mean score is multiplied by 20 to obtain a score, with a range of 0 (extremely low functioning) to 100 (high functioning). A higher MDADI score represents better day-to-day functioning and QOL.

The Functional Intraoral Glasgow Scale This is a self-assessment questionnaire for the assessment of speech, chewing and swallowing, validated in oral cancer patients. It consists of an ordinal five-grade scale marked for speech as: always understandable (5), needing repetition sometimes (4), needing repetition many times (3), understandable only by relatives (2), incomprehensible (1); for chewing as (5) any food, no difficulty (4) solid food, with difficulty (3) semisolid food, with no difficulty (2) semisolid food, with difficulty (1) cannot chew at all, and for swallowing as (5) any food, no difficulty (4) solid food, with difficulty, (3) semisolid food only, (2) liquids only (1) cannot swallow at all. This very simple scale showed good correlation with a conversational understandability test performed by speech and language therapists and with an objective computer-based method of speech analysis.[77]

BOX 28.4 Swallowing outcomes

QUESTIONNAIRE BASED MEASURES
- Sydney Swallow Questionnaire (SSQ)[69, 70]
- SWAL-QOL and SWAL-CARE[71]
- MD Anderson Dysphagia Inventory (MDADI)[72]

PERCEPTUAL MEASURES
- Blue dye test
- Water swallow test

INSTRUMENT-BASED MEASURES
- Videofluoroscopy
- Functional endoscopic evaluation of swallowing (FEES)
- Flexible endoscopic evaluation of swallowing with sensory testing (FEESST)
- Electromyography

PERFORMANCE SCALES
- Performance Status Scale for Head and Neck
- The Functional Intra oral Glasgow Scale

Perceptual measures

The simplest assessments are direct bedside clinical assessments.[78] However, these are not standardized and offer poor reliability when used alone. The use of a defined volume of water – 30 ml and looking for abnormal voluntary cough, post-swallow cough or throat clear or voice has been shown to have about a 50% sensitivity and 80–92% specificity for aspiration,[69, 70, 79] and is a useful adjunct to instrumental testing.[71] In the HNC population, water swallow test (WST) using 100 ml has been found to be 67% sensitive but less specific (46%).

Instrument based assessment of swallowing

Videofluoroscopy Videofluoroscopy remains the most frequently applied assessment of complex swallow problems as it allows assessment of anatomy and co-ordination in movements of the oropharyngeal and oesophageal stages of swallowing. It is, however, a relatively expensive and time-consuming investigation involving a multiprofessional

team from radiology, SLT and ENT. There are therefore limited opportunities for repeat assessments.[72, 80, 81] Assessments of the reliability of videofluoroscopy show superior accuracy for aspiration than for determination of pathophysiology. The situation is improved with group discussion. The application of protocols and use of frame-by-frame analysis seems inconsistent.[82–84]

In the most expert of hands, semiquantitative estimates of swallow performance can be made. The most usual of these is the oropharyngeal swallow efficiency (OPSE) calculated using the formula:

> % bolus transfer to upper oesophagus/oropharyngeal transit time.

Efficiency as a measure of swallow is based on the maximum estimated percentage (proportion) of bolus left in the pharynx and can be measured on different textures.

The penetration–aspiration scale (**Box 28.5**) assesses the presence and depth of invasion of material entering the airway, and the patient response to the aspiration and the ability to eject any misdirected material.[85, 86] Traditionally, patients aspirating more than 10% of any bolus should be restricted from taking the relevant consistency orally. Manoeuvres can be tested to reduce aspiration. Ongoing aspiration is seen in 44% patients non-laryngectomy survivors of HNC at 5 years and is associated with lower scores on a number of QOL scales.[87]

DIGEST (Dynamic Imaging Grade of Swallowing Toxicity)[88] is a validated tool for SLT to grade dysphagia after radiotherapy. It combines an assessment of efficiency (E 0–4) and of safety (S 0–4), using maximum percent of pharyngeal residue and maximum penetration–aspiration scale score. A DIGEST grade is given to the dysphagia in line with the CTCAE (common terminology criteria for adverse events) scoring D 0–4.

BOX 28.5 Penetration–Aspiration Scale[89]

Score	Criteria
1	Material does not enter the airway
2	Material enters the airway, remains above the vocal folds, and is ejected from the airway
3	Material enters the airway, remains above the vocal folds and is not ejected from the airway
4	Material enters the airway, contacts the vocal folds and is ejected from the airway
5	Material enters the airway, contacts the vocal folds and is not ejected from the airway
6	Material enters the airway, passes below the vocal folds and is ejected into the larynx or out of the airway
7	Material enters the airway, passes below the vocal folds and is not ejected from the trachea despite effort
8	Material enters the airway, passes below the vocal folds and no effort is made to eject

Fibre-optic endoscopic evaluation of swallowing (FEES)

Fibre-optic endoscopic evaluation of swallowing[90] has emerged over the past two decades as not only a complement to videofluoroscopy, but as a useful investigation in its own right. This test can be performed at the bedside and is best if a digital recording is made. Different textures of foodstuffs can be given, which can be dyed with food colouring to enhance visibility. Bolus flow during swallow, laryngeal penetration and aspiration and post-swallow residue should be assessed. The main disadvantage of FEES is that swallowing dynamics are obscured by obliteration of the view as the endoscope tip opposes pharyngeal and laryngeal musculatures during hyolaryngeal excursion.

Assessment of FEES using the penetration aspiration scale developed for videofluoroscopy can achieve good agreement between raters in 97% of cases.[91] Sharing the video image with the patient offers additional therapeutic opportunities through visual biofeedback as the patient observes the impact of swallowing manoeuvres or head positions on their swallow performance. Endoscopic swallow evaluation is relatively cheap, yet only a small minority of speech and language therapists have access to the procedure.[80] FEES should be incorporated into follow-up for HNC patients, as it can be performed by the speech and language therapist and allows for assessment of recurrence and function.

Flexible endoscopic evaluation of swallowing with sensory testing (FEESST) allows more specific assessment of sensory and motor components than in a standard endoscopic evaluation. Patients with absent pharyngeal motor function combined with poor pulmonary reserve and diminished or absent laryngeal sensation are expected to aspirate. Patients with completely insensate laryngopharynx are at extremely high risk of aspiration. Moderate sensory deficits will also result in aspiration if there is a coexisting motor dysfunction.[89]

Electromyography Surface electromyography (sEMG) signals have been used to identify swallow events.[92] The full application of sEMG has yet to be established. At least in the short term, the principal value of the technique in head and neck patients probably is as an adjunct to biofeedback and rehabilitation manoeuvres.

Performance scales designed specifically for the head and neck patient population

Performance Status Scale for Head and Neck Cancer Patients

The Performance Status Scale for Head and Neck (PSSHN)[93] is a clinician-rated scale, designed specifically for the head and neck population and the unique areas of dysfunction experienced by this group of patients. It has three domains: (1) understanding of speech, (2) normalcy of diet and (3) eating in public. There is a score from 0 to 100 for each domain. A higher score correlates with better functional ability. There is strong correlation between the PSSHN and MDADI at multiple time points.[94]

BOX 28.6 Instruments to assess comorbidity

- Kaplan–Feinstein Index (KFI)[96]
- Adult Comorbidity Evaluation (ACE-27)[97]
- Charlson Comorbidity Index (CCI)[98]
- Washington University Head and Neck Co-Morbidity Index (WUHNCI)[81]
- American Society of Anesthesiologists (ASA) Risk Classification

COMORBIDITY

Comorbidity refers to disease that coexists with and is unrelated to the index disease, and has been shown to play a major role in the treatment, outcome and prognosis of a number of malignancies. While comorbidity is used to predict outcome and may play a role in decision-making for treatment, it does not strictly qualify as an outcome measure. However, it has a significant influence on oncological and functional outcomes and is thus included in this chapter.

In 1948, the first attempt to quantify the performance status of patients with advanced cancer was made by Karnofsky.[95] Since then, a variety of instruments have evolved to measure comorbidity (**Box 28.6**).

Kaplan–Feinstein index

The Kaplan–Feinstein index (KFI) was developed for assessment of comorbidity on outcome in diabetes mellitus and has been used to study the impact of comorbidity in several cancers.[96] Information is taken from notes review and specific diseases are classified and a score given of mild, moderate or severe according to severity of organ decompensation. Where multiple comorbidities are present, an overall score is assigned according to the highest ranked illness, and where there are two or more moderate outcomes the overall score is defined as severe.

Adult comorbidity evaluation

Adult comorbidity evaluation (ACE-27)[97] is a modification of the KFI, validated and especially designed for patients with cancer. An overall score of 1, 2 or 3 is assigned according to the highest ranked single condition, except where two or more grade 2 illnesses occur in different organ systems where a score of 3 is given. The National Cancer Intelligence Network in the UK recommends the collection of ACE-27 for all cancer patients.

Charlson comorbidity index

The Charlson comorbidity index (CCI)[98] is a weighted sum of the presence or absence of each of 19 conditions. Each condition is assigned a weight from 1 to 6, where a higher value indicates more severe disease. The index is the sum of all the weights.

Washington University Head and Neck Comorbidity Index

The Washington University Head and Neck Comorbidity Index (WUHNCI)[98] is a head and neck specific tool. It takes into account seven common comorbid conditions based on their relative prognostic significance in HNC patients.

Comorbidity and HNC

HNC patients have a high prevalence of comorbidity (21–35%) due to the long-term effects of smoking and alcohol, second only to lung cancer (40%). Several studies have shown the importance of comorbidity on outcome and the prognosis of HNC.[99–103] It is an independent prognostic indicator even when age and TNM stage have been controlled for.[97]

The KFI has been found to be most successful in stratification of survival analysis in HNC patients when compared with the CCI.[100] The CCI is simple to use and has been used to evaluate comorbidity in laryngeal cancer[104] and thyroid cancer,[105] and has been validated against the ACE-27 for use in HNC.[106] However, because answers evaluate the presence or absence of disease rather than severity, it has been found to be less sensitive than the ACE-27 in assessing comorbidity.[107, 108] Comorbidity assessed through the ACE-27 has been shown to have a direct impact on HNC survival especially in the early years after survival where the greatest impact is seen in the younger patient. Comorbidity is associated with an adverse influence on disease-free survival, a higher risk of more severe complications of treatment, has an adverse effect on QOL and increases the cost of treatment.[109–112]

Comorbidity data add valuable prognostic information that may influence treatment modality. Use of single sources alone may result in some misclassification of comorbidity. Enhancing data extracted from notes with a patient self-report questionnaire can improve the accuracy of comorbidity grading.[113]

PATIENT PRIORITIES FOR TREATMENT OUTCOMES

An early classic paper on the cost utility analysis of the treatment of advanced laryngeal cancer by radiotherapy and laryngectomy presented a trade-off of QOL (retention of laryngeal speech) vs quantity of life (improved survival after primary laryngectomy) to a group of healthy (non-medical) volunteers. In order to maintain natural speech, approximately 20% of those questioned would have chosen radiation instead of surgery.[114] This paper was innovative and influential in suggesting that for some people quality, not quantity, of life was more important. But in a very recent study in a population demographically matched to HNC patients, many participants indicated that larynx conservation was not their primary consideration in treatment choice. Thirty-eight per cent of participants opted for a primary laryngectomy and the functional outcome of treatment had a greater effect than treatment modality on the utility value assigned to laryngeal cancer health state outcomes.[115] In contrast, in a paper by DeSanto et al 20% of patients expressed themselves willing to accept a reduced life span in order to preserve their larynx and QOL.[116] However, 46% of the healthcare professionals questioned had felt that the patients would accept this trade off. A study published by List et al showed that both

patients and nonpatients ranked 'being cured of cancer', 'living as long as possible' and 'having no pain' most frequently in the top three of 12 statements.[117]

There are also differences in the perception of the relative importance of different categories of symptom between patients and carers. In 1992, Mohide et al[1] demonstrated that carers ranked impaired communication and self-image/self-esteem as the two most important QOL outcome domains following laryngectomy. The patients themselves ranked the physical symptoms of tracheal mucus production and interference with social activities as the two most important items. It is important to bear this lack of correlation between patient and carer priorities in mind when counselling patients about treatment options.

Blanchard et al[118] performed a systematic review of patient preferences in HNC, defined by the subsite of the primary cancer. This study showed that whilst there was homogeneity in the methods and conclusions of studies of laryngeal preservation, studies of other subsites suffered from significant heterogeneity, thus making it difficult to draw conclusions about patient priorities. However, survival consistently trumped functional outcomes, underscoring the importance of high survival rates in contemporary or experimental treatments, whatever the subsite.

HNC are heterogenous in their biological nature, and therefore tumour behaviour and response to treatment. Furthermore, the incidence and severity of adverse effects of treatments is highly variable between patients. In their analysis of RTOG 0522 Ang et al[119] support a strategy of refining study populations, for better biologically defined HNC entities. The identification, selection and reporting of disease-specific and appropriate endpoints is therefore a research priority.

BEST CLINICAL PRACTICE

- ✓ Measurement of Base line and post-treatment swallow outcomes using a combination of clinical and instrumental assessments and validated patient outcome measures such as MDADI or PSSHN and instrumental assessments such as 100 ml water swallow test and FEES.
- ✓ Measurement of voice outcomes following treatment for early laryngeal cancer using questionnaires such as VHI short-form 10 or VoiSS.
- ✓ Collection and recording of comorbidity data WHO and ACE 27 in all head and neck cancers registered (as per National Cancer Intelligence Network guidance in UK).
- ✓ Recording of early and late toxicities associated with treatments for head and neck cancer to allow for the comparison of interventions when there is equipoise for survival.

FUTURE RESEARCH

- ➤ Development of a tool to assess xerostomia following treatment in HNSCC with a view to identifying if new treatments reduce this debilitating side effect.
- ➤ Development of a PROM for evaluation of shoulder dysfunction following treatment for HNSCC.
- ➤ Standardization of outcome measurements collected to allow for useful comparison and evaluation.
- ➤ Development of a validated scale for perceptual evaluation of alaryngeal speech.

KEY POINTS

- Outcome measures are integral to the management of patients with HNC and can relate to survival or function. Choice of appropriate outcome measures is essential.
- Numerous tools exist for assessment of voice. Self-assessment questionnaires are most commonly and easily obtained. These can be combined with perceptual and acoustic measures; the latter are commonly used as research tools.
- It is important to distinguish voice from speech since these are different concepts, thus needing different measures.
- Dysphagia is perceived by patients to be one of the most important functional outcomes of HNC treatment. Assessment should be embedded in routine practice and form part of follow-up. This should include questionnaire-based tools such as MDADI or PSSHN and instrumental assessment with FEES. VF is an outcome tool in the research setting, but also valuable in managing patients with swallowing problems.
- Comorbidity assessment using ACE-27 is recommended by NCIN for all cancer patients.

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CHAPTER 29

APPLICATIONS OF ROBOTICS IN HEAD AND NECK PRACTICE

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SEARCH STRATEGY

Data in this chapter may be updated by a search of MedLine and PubMed using the following keywords: head and neck cancer and transoral robotic surgery.

TECHNOLOGY AND OTOLARYNGOLOGY

Surgical innovation and skillfully adapting new technology to improve patient care has been part of the fabric and culture of otolaryngology, head and neck surgery since its inception. As such, there is a long history of otolaryngologists creating and embracing new surgical technology, dating back to 1921, when Dr. Carl Nylen, a Swedish otolaryngologist, used the world's first monocular operative microscope, for the treatment of chronic otitis media.[1] The next year, Dr. Gunnar Holmgren, Dr. Nylen's chief, introduced the first binocular microscope by attaching a light source to an existing Zeiss dissecting microscope.[1] In the 1970s, Dr. Walter Messerklinger and his protégé, Dr. Heinz Stammberger in Graz Austria pioneered the technique of endoscopic sinus surgery, later popularized and refined by Dr. David Kennedy in the US.[2] These noble traditions shows that otolaryngologists, head and neck surgeons are endoscopic surgeons, pioneering new techniques to improve surgical outcomes and patient care.

Recently, the introduction of surgical robotics has transformed the practice of surgery. With robotic surgery, the surgeon and his hands are physically separate from the patient. Real surgery is performed in a virtual environment, allowing the surgeon to interact with surgical anatomy with a novel perspective, in otherwise inaccessible places and in ways that would not be possible without this innovation. In 2007, the Society of American Gastrointestinal and Endoscopic Surgeons and the Minimally Invasive Robotic Association defined 'robotic surgery' as 'a surgical procedure or technology that adds a computer technology-enhanced device to the interaction between a surgeon and a patient during a surgical operation and assumes some degree of control heretofore completely reserved for the surgeon.'[2]

Currently, the daVinci® Surgical System (Intuitive Surgical Inc., Sunnyvale, CA) is the most popular platform for robotic surgery. It consists of three parts: a 'patient-side' cart deploys surgical instruments placed by the surgeon within the patient's body including a binocular 12 mm endoscope with dual zero or thirty degree optics, and a 'surgeon's console' which is remotely placed where three-dimensional surgical anatomy is recreated and linked to instruments in a virtual environment. The surgeon's console consists of a three-dimensional display, a seat for the surgeon, foot pedals to control cautery and other instruments, and hand controls linked to instruments placed in the operative field. The three-dimensional display affords the surgeon unprecedented perspective and visualization of surgical anatomy along with the ability to operate with 540 degrees of wristed instrumentation at zero or thirty degree angles. Motion scaling increases precision by eliminating tremor and fatigue while also reducing greater hand movements. The 'vision cart' houses the video processor and screens to project the procedure, primarily used by the operating assistant and the other observers.

ROBOTIC SURGERY

Transoral robotic surgery

Melder and McLeod performed the first robotic procedure in otolaryngology at the Walter Reed Army Medical Center in 2003, removing a vallecular cyst.[3] With the first generation 'standard' DaVinci® Surgical System (Sunnyvale, CA),

Hockstein, Weinstein, and O'Malley presented a series of landmark papers beginning in 2005 defining the field of transoral robotic surgery (TORS).[4–7] Whereas Melder and McLeod placed robotic arms through a slotted laryngoscope, Hockstein et al. placed the robotic arms through the oral retractors, moving from laryngoscopes to the Feyh-Kastenbauer (FK), Crowe-Davis, McIvor, or Dingman, which provided excellent exposure for the oropharynx but even allowed access to the supraglottic larynx and occasionally the hypopharynx. Different combinations of retractors, laryngoscopes, endoscopes and microsurgical instruments were used to identify the optimal setup for robot-assisted head and neck surgery. Hockstein found that placing the robotic arms through a tubed laryngoscope, such as the Lindholm, significantly limited range of motion, but that an oral and oropharyngeal retractor, such as the McIvor, provided relatively free motion of the surgical instruments and endoscope for procedures of the oropharynx, supraglottis and hypopharynx.

The operative arms carry interchangeable 5 or 8 mm diameter instruments including atraumatic forceps, monopolar cautery, bipolar cautery, among other manipulators and dissectors. The most common cutting device is the monopolar electrocautery spatula, which doubles as a dissector. Lasers have recently been adapted to work with the robot manipulators and have been a popular addition. Fibre laser technology couples the unsurpassed visualization with a more precise cutting device with nominal thermal damage and reduced tissue necrosis when compared to the monopolar electrocautery. In addition to two operative arms, either an 8.5 or 12 mm binocular stereoendoscopy or camera provide a high-definition three-dimensional view of the anatomy of the laryngopharynx (**Figure 29.1**).

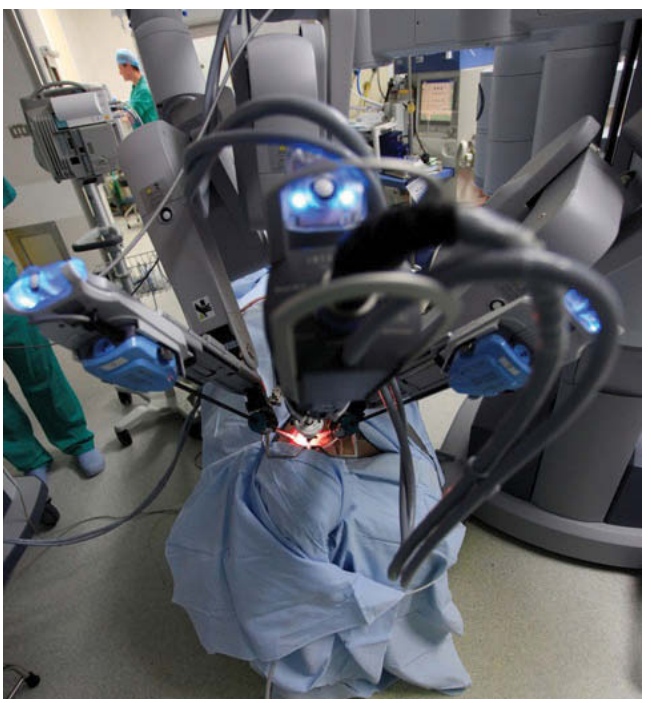


Figure 29.1 A bird's eye view of the da Vinci Si system docked in the mouth prior to TORS.

O'Malley et al. in 2006[8] demonstrated the use of TORS in cadaver and animal models. Once they had demonstrated adequate exposure with these models, they proceeded with 3 tongue base cancers on human subjects under an institution review board approved human trial. They concluded 'TORS provided excellent three-dimensional visualization and instrument access that allowed successful surgical resections from cadaver models to human patients'.[8]

Multiple studies emerged demonstrating the feasibility of transoral robotic surgery for patients with laryngopharyngeal cancer. Moore et al. reported on the feasibility of robotic surgery in a prospective case study of 45 patients with previously untreated oropharyngeal squamous cell carcinoma.[9] His case series included T1–T4a tumours with simultaneous unilateral or bilateral neck dissection. Margins were all negative, operative time improved as operative experience developed, and all 14 patients who underwent tracheostomy tube placement were decannulated. All 30 patients who had either a nasogastric or gastrostomy feeding tube placed eventually had their tubes removed. Weinstein et al.[10] in a multicentre prospective case series reported on the safety, feasibility and adequacy of surgical margins for transoral robotic resections. A total of 192 patients were initially screened and 177 were finally included, as 13 were excluded for inadequate exposure with TORS and 2 who were switched to an open approach. Most cases were oropharyngeal followed by laryngeal squamous cell carcinoma. In regard to safety, there were no intra-operative mortality or deaths in the immediate post-operative period. Blood loss averaged 83 mL and no patients required transfusions. Twenty-nine patients (16%) experienced serious adverse events requiring intervention or hospitalization. Twenty-two patients (2.3%) had a tracheostomy tube at last follow-up visit and the gastrostomy tube dependence rate was 5.0%. The positive margin rate was 4.3%. This multicentre study concluded that TORS was safe and feasible.

White et al. reported on the 1- and 2-year survival rates after transoral robotic surgery.[11] Eighty-nine patients from 2 institutions were included, mostly with oropharyngeal squamous cell carcinoma followed by laryngeal squamous cell carcinoma. T-stage ranged from T1 to T4 with most being T1 or T2 and most were overall stage III or IV. At last follow-up and after a median follow-up of 26 months, 82 had no evidence of disease, 2 died of disease, and 4 were alive with disease. The 2-year recurrence free survival rate was 86.5% and none of the patients were gastrostomy tube dependent.

Despite multiple studies and meta analyses[12] supporting the use of transoral robotic surgery, there are no randomized studies comparing surgical management of oropharyngeal carcinoma to chemoradiation. **Table 29.1** summarizes ongoing trials worldwide, aiming to identify the role of transoral surgery (with the laser or the robot) in this setting on TORS in the world, 4 of which are randomized trials. The RTOG 1221 randomized trial has been designed to compare transoral resection of p16- oropharyngeal carcinoma followed by risk-based adjuvant therapy (60 Gy IMRT with or without weekly cisplatin)

TABLE 29.1 TORS trials currently ongoing (as of January 2017)

Name of trial	Identification number	Inclusion criteria (disease specific)	Comparative arms	Primary outcome measure	Negative margin threshold
'CompARE' Phase III randomized controlled trial comparing alternative regimens for escalating treatment of intermediate and high-risk oropharyngeal cancer	ISRCTN41478539	• OPSCC in base of tongue and tonsil with MDT recommendation for treatment with definitive concurrent chemoradiotherapy • Intermediate risk [HPV +ve OPC with N2b+ disease and greater than 10 pack year history of smoking] or high risk (HPV–ve OPC) as per Ang classification	**Arm 1 (control):** Concomitant chemoradiotherapy (70 Gy in 35# and cisplatin) +/– post- treatment neck dissection **Arm 2:** Induction chemotherapy (docetaxel, cisplatin and 5-FU), followed by arm 1 **Arm 3:** Dose-escalated chemo radiotherapy (64 Gy in 25# and cisplatin) +/– post- treatment neck dissection **Arm 4:** Resection of primary and selective neck dissection plus post-operative chemoradiotherapy (T1/2 transoral surgery, T3/4 transoral or open surgery)	• Overall survival (OS) • Disease-free survival (DFS)	not specified

'PATHOS'
A phase II/III trial of risk-stratified, reduced intensity adjuvant treatment in patients undergoing transoral surgery for HPV +ve OPC
	NCT02215265	• Stage T1–T3, N0–N2b SCC of the oropharynx
		• HPV +ve
			Post-operative risk stratification
			1. Low risk: no adjuvant treatment
			2. Intermediate risk: randomized to:
			  • 50 Gy in 25#
			  • 60 Gy in 30#
			3. High risk – randomized to:
			  • 60 Gy in 30#
			  • 60 Gy in 30# with cisplatin
				• Patient-reported swallowing outcome	> 5 mm

'ADEPT' Post-operative adjuvant therapy de-intensification trial for HPV-related, p16+ oropharynx cancer	NCT01687413	• Patient must have histologically confirmed p16 positive SCC of the oropharynx (OPSCC). • Patient must have undergone transoral resection of their T1–4a oropharynx primary to a negative margin, and a neck dissection(s). • Patient's disease must be pathological N-stage positive. • Patient's disease must show ECS in their nodal metastasis verified by central pathologist's review. • Patients with synchronous primaries are included. • Patients with unknown primaries are included if the diagnosis and resection of a primary site in the oropharynx is made from an endoscopic or robotic surgical procedure(s)	Post-operative randomization **Arm 1:** 60 Gy in 30# **Arm 2:** 60 Gy in 30# and cisplatin	• Disease-free survival (DFS) • Locoregional control	not specified

(Continued)

TABLE 29.1 ***(Continued)*** TORS trials currently ongoing (as of January 2017)

Name of trial	Identification number	Inclusion criteria (disease specific)	Comparative arms	Primary outcome measure	Negative margin threshold
'ORATOR' A phase II randomized trial for early-stage SCC of the oropharynx: radiotherapy vs transoral robotic surgery	NCT01590355	• Histologically confirmed SCC primary tumour site in the oropharynx • Tumour stage: T1 or T2, with likely negative resections at surgery • Nodal stage: N0, N1, or N2, without extranodal extension on pre-randomization imaging	**Arm 1:** Radiotherapy +/– chemotherapy **Arm 2:** Transoral Robotic surgery and neck dissection +/– adjuvant radio(chemo)therapy based on pathological findings	• Quality of life	>2 mm
'ECOG 3311' Transoral surgery followed By low-dose or standard-dose radiation therapy with or without chemotherapy in treating patients with HPV Positive Stage III-IVA oropharyngeal cancer	NCT01898494	• SCC or undifferentiated carcinoma of the oropharynx; patients must have been determined to have resectable oropharyngeal and neck disease • Patients must have AJCC TNM tumour stage III, IV a, or IV b (with no evidence of distant metastases) • Nodal stage N1-N2b • p16 (HPV) positive disease	Post-operative risk stratification 1. Low risk: no adjuvant treatment 2. Intermediate risk: randomized to: • 50Gy in 25# • 60Gy in 30# 3. High risk: chemoradiotherapy	• Progression free survival rate • Accrual rate • Risk distribution • Incidence of grade 3–4 bleeding events during surgery and positive margins after surgery	>3 mm
A single-arm phase II Study of post-transoral robotic surgery (TORS) alone to the primary tumour site and SND followed by adjuvant radiation therapy (+/– chemotherapy) to the regional nodes for advanced stage, HPV positive, oropharyngeal cancer	NCT02159703	• Histologically confirmed diagnosis of SCC of the oropharynx, stage IVa, p16-positive on immunohistochemistry • Pathologic T1 or T2 disease, resected with negative margins (2 mm) • Pathologic N2a, N2b, or N2c disease		Number of adverse events	>2 mm
Robotic surgery for oropharyngeal SCC	NCT02225496	• Patients with a previously untreated, T1 or T2, N0-N2b transorally resectable (as determined by the treating surgeon), histologically proven HPV positive, SCC of the oropharynx		Time to local-regional recurrence (TTLRR)	>5 mm
Transoral robotic surgery in treating patients with benign or malignant tumours of the head and neck	NCT01473784	• Patient must present with indications for diagnostic or therapeutic approaches for benign and/or malignant diseases of the oral cavity or laryngopharynx		Determine the feasibility of the TORS in patients with oral and laryngopharyngeal benign and malignant lesions	not specified

SCC, squamous cell carcinoma; SND, selective neck dissection, HPV, human papilloma virus; ECS, extracapsular spread.

to standard chemoradiation therapy (70 Gy IMRT with weekly cisplatin); owing to reduced numbers of HPV- disease, this trial failed to meet recruitments targets, and has been closed. In the UK, the CRUK funded ComPARE trial will recruit surgically resectable intermediate and high-risk patients as per the stratification data published by Ang et al.[13] and has a surgical resection followed by platinum based RT as one of the arms.

Additionally, while HPV-associated oropharyngeal carcinoma has been clearly shown to have improved prognosis compared to HPV negative oropharyngeal carcinoma, no trials have yet been conducted on de-escalation of therapy. Accrual for ECOG 3311 is currently underway, which is a phase II randomized trial comparing low-dose radiation (50 Gy) vs standard post-operative dose of radiation (60 Gy) after transoral resection of of p16+ oropharyngeal squamous cell carcinoma with intermediate risk factors (< 3 mm margins, < 1 mm ECS, and 2–4 metastatic lymph nodes). Patients with low-risk features (T1–T2, N0-1, and negative margins) will receive no post-operative adjuvant therapy and patients with high-risk features (> 1 mm ECS, > 5 metastatic lymph nodes, or positive margins) will receive standard 66 Gy IMRT with weekly cisplatin.

In the UK, the PATHOS trial will recruit patients with low and intermediate staged HPV positive oropharyngeal cancer, managed by transoral excision followed by risk stratified radiation therapy. This trial aims to establish whether the de-intensification of adjuvant treatment in patients undergoing TLM/TORS for HPV-positive OPC, by reducing radiation dose or omitting chemotherapy, will confer improved swallowing outcomes at 1-year post-treatment whilst maintaining high cure rates. Thus, the treatment of this disease is rapidly evolving and significant changes can be expected in the next decade. A summary of these trials can be found in a recent review[14] TORS has also been shown to have a clear role in resection of supraglottic[15, 16] and hypopharyngeal cancers.[17–19] A new role has been defined for TORS in diagnosing the unknown primary, using tongue base mucosectomy, where pick-up rates of between 50% and 60% have been demonstrated,[20] even in patients who show no avidity on CT-PET imaging.[21]

Transoral robotic surgery versus transoral laser microsurgery

Transoral laser surgery has been shown to be effective in the management of tonsil tumours and is discussed at length in Chapter 22, Transoral laser microsurgery. The principles of this procedure involve resection of the tumour by following its extent, tailoring resection to each patient. Assessment of the depth of the tumour is achieved frequently by transecting the tumour until the 'normal' tissues are reached. The cutting characteristics of the laser mean this is clearly demonstrable. However, margins on the specimen are frequently reported as close and marginal biopsies are therefore used to assess status. While this approach is oncologically safe, it can present practical concerns in deciding if adjuvant therapy is needed.[22] Nevertheless, the significant amount of work in the TLM literature has paved the way to establish TORS for tonsil tumours as *bonafide* management with firm long-term oncological outcomes.

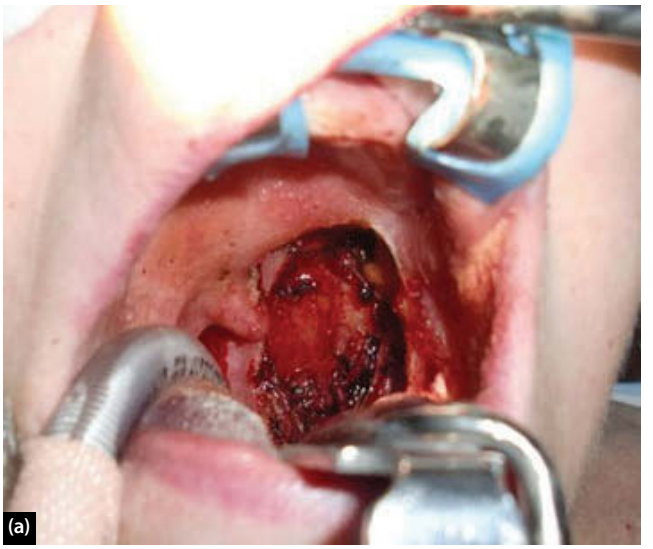
The principle of TORS surgery is *en bloc* resection with a clear margin (**Figure 29.2**). The foundations for *en bloc* resection of tonsil cancers via a transoral route had been laid back in the 1950s when P-C. Huet described this procedure.[23] This involved transoral resection of the tonsil and the superior constrictor muscle deep to the parapharyngeal space. Holsinger et al.[24] reported good outcomes for tonsil tumours with this technique. *En bloc* resections of the tonsil, although feasible with the TLM approach, are not easy due to the line of sight working and instrumentation. The advent of TORS has allowed surgeons to perform *en bloc* resections at this primary site. The superior optics and manoeuvrability combined with the ergonomics have meant that the learning curve for transoral robotic radical tonsillectomy is not as shallow as that of transoral laser microsurgery (**Figure 29.3**).

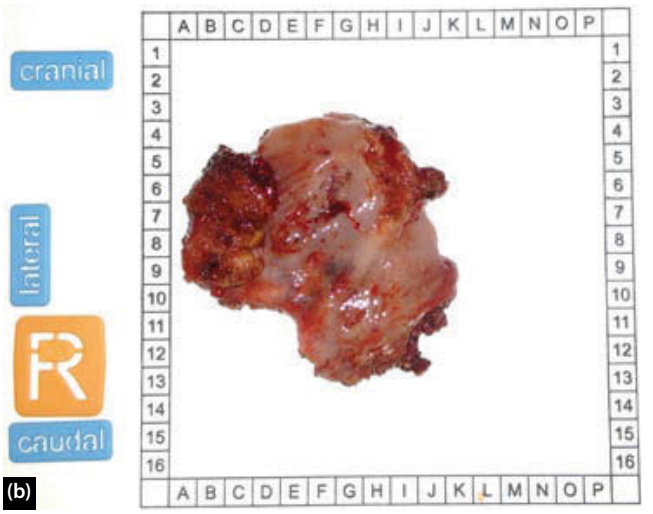
Robotic thyroidectomy

Transoral endoscopic head and neck surgeons rely on access through the mouth and axilla which provides ample opportunity for innovation and improvement in minimally invasive techniques for the treatment of laryngopharyngeal tumours. However, robotic surgery may also play a role for the management of tumours of the thyroid and parathyroid.

Advances in minimally invasive thyroid surgery date back to 1996 with the first endoscopic parathyroidectomy performed by Gagner.[25] The operative setup resembled that of laparoscopic surgery utilizing 5 mm laparoscopic instruments placed between the platysma and strap muscles with the operative space maintained with CO_2 insufflation. Subsequent advances involved minimally invasive video-assisted thyroidectomy (MIVAT) in which the thyroid gland is removed with or without gas insufflation via cervical, axillary, or anterior chest wall approaches.[26, 27] Multiple Asian studies have emerged reporting on endoscopic transaxillary thyroidectomy.[28–30] Chang et al. reported their experience with a combined endoscopic-robotic transaxillary approach for thyroidectomy.[31] Kang et al. reported on 200 patients who underwent transaxillary robotic thyroidectomy utilizing the DaVinci® Surgical System.[32] The combination of minimally invasive thyroid surgery utilizing the DaVinci® Surgical System provides many advantages for the endoscopic head and neck surgeon. The three-dimensional display employing 30-degree optics along with the 540 degrees of wristed instrumentation improve operative dexterity along with operative field exposure and visualization.

Terris et al.[33] demonstrated the use of robotic-assisted thyroidectomy via a facelift incision. In 2012, he demonstrated the feasibility of the facelift approach, comparing it favourably against transaxillary robot-assisted thyroidectomy. Specifically, in his series of 15 patients, he demonstrated decreased operative time and outpatient thyroidectomy





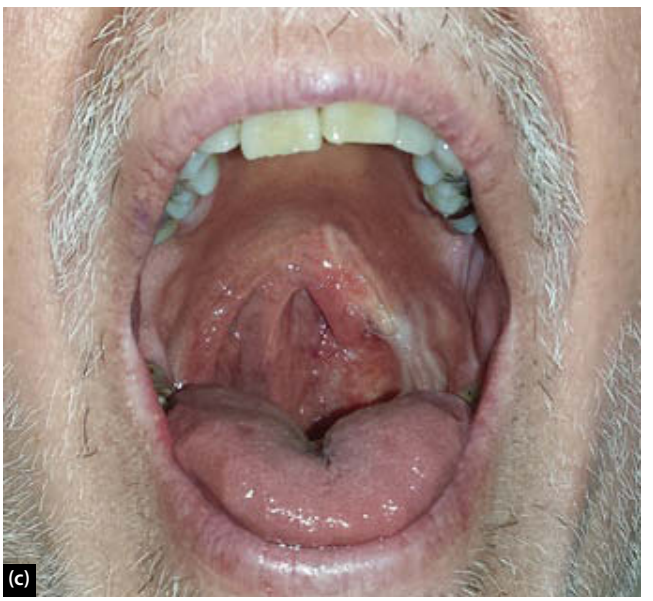


Figure 29.2 **(a)** is the view following transoral robotic *en bloc* resection of a T2 tonsil cancer. **(b)** is the specimen with the cancer in the middle and demonstrates adequate macroscopic margins. **(c)** shows a fully healed lateral oropharygectomy defect.

Figure 29.3 Photograph shows robotic surgery in progress, with dual surgical consoles. The two console surgeons share the same view and can swap control of the instruments, which facilitates training and allows rapid acquisition of skills.

without drain placement in robotic facelift thyroidectomy compared to transaxillary thyroidectomy. A recent meta-analysis of 5200 patients showed an equivalent adverse event and complication rate for robotic thyroidectomy compared to conventional approaches, generating confidence in wider adoption of the technique.[34] Many, however, remain sceptical of robotic-assisted techniques in thyroidectomy given that the time-honoured approach of conventional open thyroidectomy remains safe and effective.

Robotic neck dissection

The neck dissection has undergone significant changes from the radical neck dissections to functional and selective neck dissections without compromising oncologic principles and outcomes. This has led to a decrease in the morbidity of neck dissection. Now, authors have demonstrated minimally invasive combined endoscopic-robotic approaches to neck dissection in human cadaver models.[35] In 2004, Werner et al.[36] successfully demonstrated management of cervical lymphadenopathy using an endoscopic approach for squamous cell carcinoma in the setting of sentinel lymph node biopsy. Also, Kang et al. demonstrated the feasibility of robot-assisted neck dissection for well-differentiated thyroid carcinoma.[37] Furthermore, in 2010 Moore et al. demonstrated the use of transoral robotic surgery for retropharyngeal lymphadenectomy in papillary thyroid carcinoma.[38] Comparative studies of open and robotic neck dissections via a retroauricular/facelift route have shown equivalent functional and oncologic outcomes, with the robotic approach taking greater time, which could be ascribed to the learning curve.[39–41]

Robotic sleep apneoa surgery

Obstructive sleep apneoa (OSA) is a serious public health problem, as it is an independent risk factor for hypertension, myocardial infarction, and stroke. Sleep surgery has

a long history of improving quality of life for patients with OSA but has been limited by exposure of the posterior oropharynx as well as longevity in post-operative improvement scores. Given the success of robotic-assisted techniques in head and neck surgery, sleep medicine seemed an appropriate extension of the previously described techniques. Many surgeons were performing base of tongue resections for malignant disease with great precision and minimal complications, thus base of tongue resections for benign disease also seemed to be an appropriate use of the robot. In 2010, Vicini reported on his experience of 10 patients who underwent transoral robotic surgery for the management of OSA due to tongue base hypertrophy.[42] He resected the base of tongue in a piecemeal fashion, starting medially and subsequently resecting laterally. Vicini had confirmed in a cadaveric anatomic study that no significant neurovascular structures were present in the midline of the base of tongue, thus beginning resection there was quite safe.[43] All surgeries were successfully completely solely with TORS and there were no serious peri-operative complications. In the preliminary novel experience, Vicini routinely performed tracheostomies prior to the tongue base resections for every patient. Mean blood loss, operative time, setup time, pre-operative Epworth Sleepiness Scale, and pre-operative AHI was 25 mL, 45.5 min, 41.4 min, 12.4, and 38.3 respectively. Post-operative Epworth Sleepiness Scale and AHI were 6.9 and 20.6 respectively. There was a mean follow-up of 6 months. Vicini successfully demonstrated the feasibility of robotic-assisted sleep surgery.

In 2012, Friedman followed up on Vicini's work by performing midline posterior glossectomies for OSA without first performing a tracheostomy.[44] He included 40 patients who underwent TORS for obstructive sleep apneoa-hypopnoea syndrome and compared them to 2 cohorts: patients undergoing radiofrequency treatment or submucosal coblation. He reported that the TORS patients took longer to recover with a longer time to resume normal diet; TORS patients also took longer than the radiofrequency treated patients to resume regular activity. But that is where TORS' weakness stopped. Reduction in AHI for TORS patients averaged 60.5% while radiofrequency treated and coblated patients experienced average reductions of 32% and 37% respectively; both of these differences from TORS were statistically significant. Furthermore, only the TORS group achieved a statistically significant improvement in minimum oxygen saturation. Friedman noted no airway or bleeding complications. Once again, the feasibility of TORS for sleep surgery was confirmed.

Not satisfied with his results for in OSA outcome compared to open tongue base reduction with hyoid epiglottoplasty as described by Chabolle, Vicini wanted to apply the concept of geniohyoidpexy with transoral robotic surgery. In 2011, Vicini reported on the success of this technique in the cadaver model.[45] The hyoid bone was identified via transoral resection through the base of tongue and subsequently dissected free of its suprahyoid attachments. With minimal further dissection, the medial inferior border of the mandible is identified and two holes are drilled. One to two stitches are placed through those holes and then around the hyoid bone under slight tension, allowing for geniohyoidpexy and successfully demonstrating TOR access to the hyoid bone, which can be useful for many other applications.

Robotic skull base surgery

In 2007, Hanna et al. published on robotic-assisted anterior and central skull base surgery in a cadaver model.[46] Hanna used bilateral sublabial incisions with bilateral Caldwell-Luc antrostomies and posterior septectomy in order to gain access to the cribriform plate, fovea ethmoidalis, medial orbits, planum sphenoidale, sella turcica, suprasellar and parasellar regions, nasopharynx, pterygopalatine fossa, and clivus. The ability to perform two-handed endoscopic closure of dural defects was a major advantage of this approach. Kupferman et al.[47] described reconstruction of the skull base following robotic resection via a bilateral translabial Caldwell-Luc approach. They undertook a robotic-assisted suture based technique for reconstruction of dural defects suggesting that traditional suture techniques can be implemented after robotic resection using robotic instrumentation.

O'Malley et al.[48] developed a transoral approach to apply robotics for the treatment of tumours of the parapharyngeal space and infratemporal fossa. Beginning with pre-clinical studies on cadaver and animal models, O'Malley demonstrated the feasibility of TORS in this setting. In February 2007, the findings from this pre-clinical work led the way to perform a robotic resection of an infratemporal fossa cystic neoplasm in a live patient, as part of a prospective human trial. The robotic approach afforded adequate and safe identification of the internal carotid artery and cranial nerves. They achieved complete resection, excellent haemostasis and there were no peri-operative complications. In the prospective study, O'Malley et al. enrolled 10 patients with benign parapharyngeal space tumours without carotid encasement and found that 9 of the 10 patients were successfully completed with TORS with acceptable blood loss and no significant peri-operative complications.[48] His approach involved dissection intraorally through the pterygomandibular raphe. Seven of the patients were treated for pleomorphic adenoma, one of these required conversion to an open approach. They noted capsule disruption in 2 and pharyngeal disruption in 2. The 7 patients with pleomorphic adenomas were tumour free during the follow-up period ranging from 16 to 37 months. The other 3 patients were treated for benign cysts. Kim et al.[49] also provided support for use of TORS for benign tumours of the parapharyngeal space and infratemporal fossa in their series of 3 patients with pleomorphic adenomas. The disadvantage of this technique is adequate exposure, ensuring complete surgical resection, which is a serious consideration when considering malignant disease.

Blanco et al. also assessed the feasibility of the DaVinci® Surgical System for infratemporal fossa and anterior skull base lesions using a cadaver model.[50] They gained access to the infratemporal fossa using a maxillary window and the anterior skull base using a maxillary window and a nasal corridor. Although they deemed the robotic-assisted approach to the skull base was feasible, they felt the DaVinci

instruments need to be redesigned to be smaller and with distal articulating tips prior to clinical application.

Robotic approaches to the anterior and midline skull base via a transoral approach was assessed in a pre-clinical trial for TORS. O'Malley et al.[51] performed 10 procedures on cadaver and animal models. While they were able to access the canine skull base using a transoral approach, for the human cadaver they noted the standard transoral approach did not provide adequate access to the midline and anterior skull base. They developed a new technique deemed cervical-transoral robotic surgery (C-TORS), which successfully provided access to the anterior and midline skull base. For the C-TORS technique, standard robotic trocars are inserted at the posterior border of the submandibular gland with the robotic instruments directed cranially, parallel to the long axis of the spine. The camera was placed transorally, however, for the end effector instruments, a 3 mm cut was made through skin and platysma at the posterior border of the submandibular gland bilaterally, then standard plastic introducers and round-tip dilators were passed through those incisions and traced upward in a circular dissecting fashion until they were visualized intraorally using the camera. The introducers pierce the pharynx at the level of the lateral hypopharynx. They describe how using their technique they do not injure arteries, veins or nerves. McCool et al.[52] also described a transcervical approach along with a transoral approach for infratemporal fossa lesions using 4 cadaver models. While O'Malley described ports posterior to the submandibular gland, McCool placed a midline suprahyoid port, which pierces into the vallecula. He reported excellent visualization into the infratemporal fossa with a 30 degree scope.

Additionally, Ozer et al. described multiple approaches involving different placement of the camera and end effector instruments along with utilization of 0 degree and 30 degree scopes in order to achieve adequate visualization of the skull base.[53] They applied transoral, transnasal, transpalatal, and transcervical approaches to determine optimal visualization. Transnasal approaches required posterior septectomies while transpalatal approaches required elevation of a mucoperiosteal flap posterior to the molar teeth and resection of a portion of the hard palate and vomer. They concluded that the transoral camera and instruments with a 30 degree endoscope provide good control over the posterior and lateral nasopharynx without good control over the roof of the nasopharynx or posterior choana. The transnasal camera (0 degree) with transoral instruments provided great visualization but with cumbersome instrumentation. Overall, they felt the transpalatal approach was the best compromise of visualization and instrumentation for the nasopharynx, clivus and anterior skull base. Transcervical ports provided superior range of motion and use of instrumentation with the camera in any of the possible configurations.

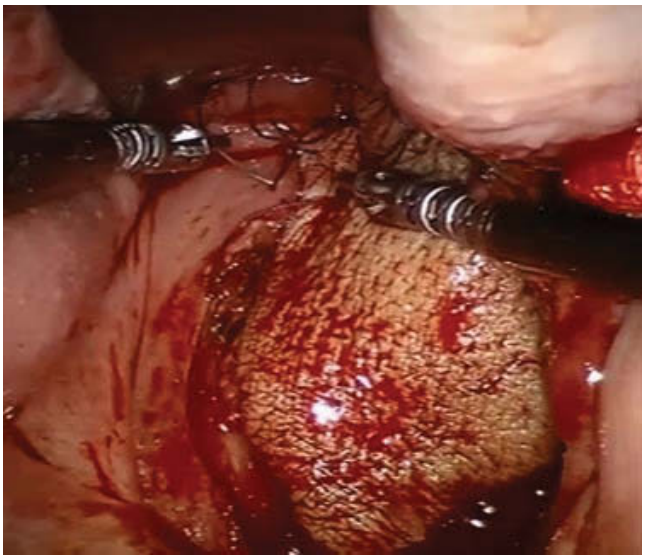


Figure 29.4 TORS free flap inset in progress following resection of a recurrent oropharyngeal cancer of the tonsil and the tongue base. A medial sural artery perforator flap was used, and the pedicle fed into the neck via the oropharyngeal defect (Courtesy of Prof Vinidh Paleri, London).

Free flap inset via TORS

TORS has allowed removal of complex tumours from the oropharynx. As acceptability of the recognition of the safety and efficacy of the procedure has evolved, larger and more complex tumours are being treated. This has increased the need to reconstruct the oropharynx to provide velopharyngeal competence and reduce fistula risk. A number of algorithms have been proposed depending on the site and size of the defect. These range from allowing healing by secondary intent to velopharyngoplasties with local flaps, local flaps alone or in larger defects regional and free-flap reconstruction. Robotic assisted mobilization and inset of the flaps have been described in extending the range of options for these patients (**Figure 29.4**).[54, 55]

CONCLUSION

Robotic technology has demonstrated great promise in the field of otolaryngology. As the technology becomes refined and instrumentation is developed for the specific purpose of head and neck surgery, robotic surgery may have an even greater impact on minimally invasive surgical outcomes.

KEY POINTS

- Significant global expertise exists in transoral robotic surgery (TORS).
- TORS is primarily used for oropharyngeal and supraglottic primaries.
- Several ongoing randomized trials on transoral surgery will clarify the role of this modality in head and neck cancer treatment.
- Improvements in technology mean that transoral surgery is here to stay.

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CHAPTER 30

BIOLOGICALLY TARGETED AGENTS IN HEAD AND NECK CANCERS

Kevin J. Harrington and Magnus T. Dillon

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SEARCH STRATEGY

Data in this chapter may be updated by a Medline search using the keywords: head and neck cancer, oncogene, tumour suppressor gene, growth factor, epidermal growth factor receptor, tyrosine kinase inhibitor, monoclonal antibody, cell cycle control, DNA damage repair and immunotherapy.

INTRODUCTION

Cancer is a genetic disease that develops when the information in cellular DNA is corrupted or wrongly decoded. This leads to altered patterns of gene expression and derangement of normal protein function. Simply stated, genetic changes leading to cancer mediate two general effects: (i) overactivity of genes that stimulate cell growth, survival and spread; and (ii) underactivity of genes that repress these processes. Through these changes, cancer cells acquire properties that allow them to grow in an uncontrolled fashion, invade adjacent normal tissues, recruit their own blood supply, avoid immune detection and destruction, spread to distant sites and develop resistance to anticancer treatments. By understanding these processes, we have an opportunity to design and implement new classes of so-called targeted therapies that will exploit the fundamental biological differences between malignant and normal cells.

ONCOGENES AND TUMOUR SUPPRESSOR GENES

The functions of two classes of genes (oncogenes and tumour suppressor genes) are central to understanding cancer biology.[1] Oncogenes represent mutated versions of normal cellular genes (called proto-oncogenes) encoding proteins that control cell proliferation, survival and spread. In normal cells, the expression of proto-oncogenes is tightly regulated but, in cancer, abnormal proto-oncogene function causes uncontrolled cell division, enhanced survival (even during anticancer treatment) and dissemination. A single mutated copy of a proto-oncogene can promote cancer (so-called phenotypic dominance). Such mutations are rarely associated with inherited cancer syndromes: *ret* proto-oncogene mutations are associated with multiple endocrine neoplasia (MEN) syndromes (types 2A and 2B) and germline mutations in *H-ras* can cause Costello syndrome (high birthweight, cardiomyopathy and cancer predisposition). Oncogenes are activated in three ways to cause cancer:

- gene mutation can change the genetic code and enhance the function of the encoded protein (e.g. *RAS* mutation)
- gene amplification results in multiple additional copies of a normal gene being present in the genome (e.g. *EGFR* amplification)
- gene translocation, which is important in salivary gland cancers, involves movement of genetic material from its normal chromosomal locus to a new position which is usually on a different chromosome.

In contrast, tumour suppressor genes (TSGs) are normal cellular genes whose function inhibits cell proliferation and survival. The function of both copies of a TSG must be lost in order to promote cancer (so-called phenotypic recessiveness). Mutated TSGs are responsible for the majority of inherited cancer syndromes, although this is not a significant cause of head and neck cancers.

THE HALLMARKS AND ENABLING CHARACTERISTICS OF CANCER

Eight key changes that drive the malignant process have been described: these 'hallmarks of cancer' are: growth factor independence; evading growth suppressors; avoiding apoptosis; maintaining replicative potential; angiogenesis; invasion/metastasis; reprogrammed energy metabolism; and evading immune destruction (**Figure 30.1**).[2] In addition, two so-called enabling characteristics of cancer (genomic instability and inflammation) have been defined.[3] These processes are described briefly below.

Growth factor independence

In normal health, activation of growth factor receptors (GFRs) is very tightly controlled, as is the synthesis and release of the ligands that stimulate them. Cancer cells overactivate normal GFR signalling pathways to promote unrestrained cell division through three main strategies: (i) they make and release growth factors to stimulate their own receptors (autocrine signalling) and those on neighbouring cells (paracrine signalling); (ii) they modify the number, structure and/or function of surface GFRs to increase the rate and duration of receptor activation (even in the absence of ligand); (iii) they deregulate signalling pathways downstream of GFRs so they are permanently turned on (constitutively active).

Insensitivity to anti-growth signals

Anti-growth signals can force cells into quiescence (G0 stage of the cell cycle) or induce their terminal differentiation, which represents a state in which they will no longer multiply. Anti-growth signalling is mediated by cell surface ligand-receptor interactions, especially through transforming growth factor beta (TGF-β) binding to TGF-β receptor. Anti-growth signalling pathways mainly control cell progression and mediate their effects through retinoblastoma protein (Rb), cyclins, cyclin-dependent kinases (CDK) and their inhibitors (CDKi). Loss of normal anti-growth signalling pathways is extremely common in head and neck cancers.

Avoidance of apoptosis

Normal cells constantly audit the balance between incoming survival and death signals. They require constant 'reassurance' from their environment in order to prevent them from activating signalling pathways that would result in their committing suicide. In normal cells, DNA damage (including that induced by radiotherapy or chemotherapy) leads to a block in proliferation (cell cycle arrest) and an evaluation of the cell's capacity for repair. If the damage exceeds the repair capacity, the balance of survival and death signals swings in favour of the death signals and the cell commits to programmed cell death (apoptosis). This mechanism guards the genome against persisting DNA damage and prevents mutations being passed to the daughters of cell division. Loss of normal apoptotic pathway signalling is an extremely common event in cancer. Indeed, the best known cancer-associated gene (*p53*) is intimately involved in controlling apoptosis and is functionally inactivated in the majority of head and neck cancers.[4,5] By circumventing normal apoptotic signalling, cancer cells are better able to sustain DNA damage without its causing cell death and are more likely to be intrinsically resistant to anticancer treatments.

Sustained angiogenesis

In normal tissues, growth of new blood vessels (angiogenesis) is held very tightly in check by a balance between stimulatory (pro-angiogenic) and inhibitory (anti-angiogenic) signals, which normally favours inhibitory signalling.

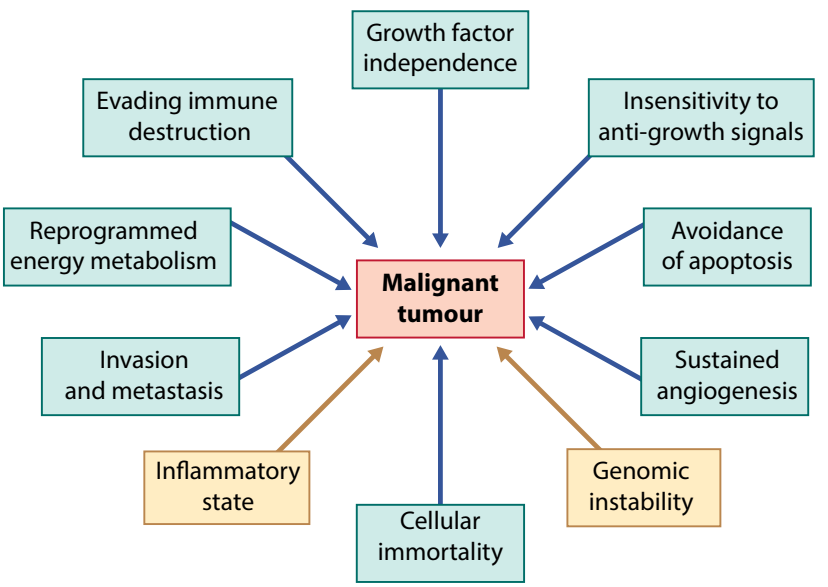

Figure 30.1 The eight hallmarks (blue boxes) and two enabling characteristics (yellow boxes) of cancer.

The growth of cancer deposits is linked to their being able to secure a dedicated blood supply. The diameter of growing cancer deposits is restricted to 60–100 μm by the diffusion limit of oxygen and nutrients from blood vessels. If a nascent tumour is to exceed this limit, it must develop its own blood supply. Cancers recalibrate the balance between pro- and anti-angiogenic factors and activate the so-called 'angiogenic switch'. To do this, they increase production of pro-angiogenic proteins, such as vascular endothelial growth factor (VEGF), and/or decrease production of anti-angiogenic proteins, such as thrombospondin-1.

Cellular immortality

Normal somatic cells can complete a finite number of cell divisions (Hayflick limit) before they permanently arrest their growth in a process of replicative senescence. This process occurs because cells cannot fully replicate the telomeric terminal portions of chromosomes at each cell division. Over time, telomeres shorten progressively, effectively behaving like molecular clocks that count down a normal cell's lifespan. In contrast, stem cells and malignant cells achieve immortality by maintaining the length of their telomeres. In most tumours, this process involves upregulation of cellular telomerase, but in 10–15% of cases a different mechanism called alternative lengthening of the telomeres (ALT) is responsible.

Invasion and metastasis

Distant metastases cause 90% of cancer deaths. A series of complex biological processes must be co-ordinated in order that metastasis can occur:[6] (i) disengagement from cellular and stromal attachments at the local site; (ii) degradation of the extracellular matrix followed by specific directional motility; (iii) invasion of blood/lymphatic vessels and tumour embolization; (iv) survival in the circulation until arrival at the metastatic site; (v) adherence to endothelium of blood vessels at the metastatic site and extravasation from the vessel; (vi) proliferation and invasion at the new location and recruitment of a new blood supply. The patterns of metastasis to specific organs are not random, but appear to be driven by expression of chemokine receptors by tumour cells that allow them to 'seek' a suitable environment in which to establish a colony.[7] Interestingly, the patterns of metastasis of human papillomavirus-positive (HPV+ve) and -negative (HPV-ve) head and neck tumours appear to be different and the underlying mechanisms of this phenomenon remain to be elucidated.

Reprogrammed energy metabolism

Chronic, uncontrolled cancer cell proliferation requires a reconfiguration of the way in which cancer cells metabolize glucose.[8] Normal cells process glucose, initially in the cytoplasm by glycolysis to yield pyruvate, and then in the mitochondria by oxidative phosphorylation to generate carbon dioxide and water. In contrast, even under oxygenated conditions, cancer cells tend to switch their metabolism to preferential use of glycolysis with generation of lactate (the so-called Warburg effect). As a consequence, they generate only two adenosine triphosphate (ATP) molecules per glucose (as opposed to a maximum of 38 via oxidative phosphorylation). As yet, the reasons for this apparently profligate use of glucose are not entirely clear but seem to provide proliferating cancer cells with a means of generating large amounts of essential metabolic precursors. This reprogramming is driven by mutations in key oncogenes and TSGs and this suggests that it is an important underlying principle of cancer biology.

Evading immune destruction

The relationship between a tumour and the immune system of the host in which it grows is immensely complex. According to the theory of immune surveillance, the immune system mounts a constant vigil against the emergence of premalignant and frankly malignant cells. The most frequently cited evidence for this comes from the observation that chronic immunosuppression (e.g. after kidney transplantation) is associated with a marked increase in specific cancers, especially those of viral origin. The immune system also appears to present a significant barrier to non-viral cancers in immunocompetent patients. However, it is clear that this function of the immune system frequently fails, as shown by the occurrence of malignant tumours. A paradigm that has been proposed to explain the interplay between an evolving tumour and the host's immune system over time is the so-called Elimination-Equilibrium-Escape model.[9] This model supposes that the immune system is frequently able to eliminate mutant precancerous/cancerous cell clones such that they never become clinically apparent. However, in some instances, the emerging tumour cells are able to suppress antitumour immune responses sufficiently to allow them to establish a state of equilibrium in which they can persist, albeit as microscopic, dormant deposits of malignant cells. Ultimately, some nascent tumour deposits will accumulate other changes (e.g. loss of tumour-associated antigens or major histocompatibility complex proteins) that will allow them to escape from immunosurveillance and emerge as clinically apparent malignancies. As part of this process, it is thought that selection of less immunogenic cancer cells (through immunoediting) and active recruitment of immunosuppressive components of the immune system (e.g. regulatory T-cells (T_{reg}) and myeloid-derived suppressor cells (MDSCs)) to some cancers allows tumours to develop and spread without becoming targets for immune clearance.

Although it is currently impossible to validate this paradigm, it provides a useful framework in which to approach the development of novel immunotherapies that may be able to target all aspects of the cancer-immune system interaction.

Enabling characteristics of cancer

The roles of genomic instability and inflammation in enabling carcinogenesis have recently been highlighted.

Genetic instability defines a state in which cancer cells lose control of the integrity of their genetic material. As such, they acquire an increasing repertoire of mutational changes that progressively alters their biology and promote the hallmarks of cancer. The second enabling characteristic describes the common situation in which premalignant and frankly malignant lesions excite an inflammatory state through the recruitment and activation of components of the immune system that promote and support tumour growth and spread.

BIOLOGICALLY TARGETED AGENTS

Huge improvements in our knowledge of the biology of cancer have opened up the possibility of developing novel targeted therapies for head and neck (and other) cancers. In this section, the review will focus on three specific themes that, at the time of writing, appear most promising. These areas are: (i) targeting growth factor independence; (ii) developing molecularly targeted drugs that enhance the response to radiotherapy (radiosensitizers); and (iii) enhancing antitumour immune responses using immunomodulatory monoclonal antibodies (MAB).

Targeting growth factor independence

Squamous cell cancers of the head and neck (SCCHN) very frequently display upregulated epidermal growth factor receptor (EGFR) signalling. EGFR is a member of the c-erbB family of transmembrane type I receptor tyrosine kinases. These receptors, comprising four members (EGFR/c-erbB-1/HER1, c-erbB-2/neu/HER-2, c-erbB-3/HER-3, c-erbB-4/HER-4),[10, 11] consist of a glycosylated extracellular ligand-binding domain, a hydrophobic trans-membrane component and an intracellular domain with tyrosine kinase activity (**Figure 30.2**). Binding of the cognate ligand to the specific ligand-binding domain on the extracellular component of EGFR leads to a cascade of intracellular secondary messengers that lead to altered patterns of gene expression, such that the binding of a protein on the cell surface is able to influence the cell's behaviour. Normally, activation of EGFR is tightly controlled, as is the synthesis and release of the ligands (transforming growth factor alpha and epidermal growth factor) that bind to it.

SCCHN achieves growth factor independence by: manufacturing and releasing growth factors that stimulate its own receptors (autocrine signalling) and those of neighbouring cells (paracrine signalling); altering the number, structure or function of the surface growth factor receptors that it displays; and by deregulating the signalling pathway downstream of the receptor. In contrast to certain tumour types where EGFR gene amplification or mutation is implicated, overexpression of the receptor, without gene amplification, is the dominant process whereby EGFR influences the pathobiology of SCCHN. A mutated form of EGFR (EGFR variant III) was reported to be present in 42% of head and neck cancers,[12] but recent reports have suggested that it does not play a major role in head and neck cancer biology.[13] The contribution of c-erbB-2 and c-erbB-3 expression to the biology of SCCHN remains unclear, but it is known that c-erbB-2:c-erbB-3 (HER2/HER3) heterodimers are potent inducers of the PI3-kinase anti-apoptotic pathway.[14]

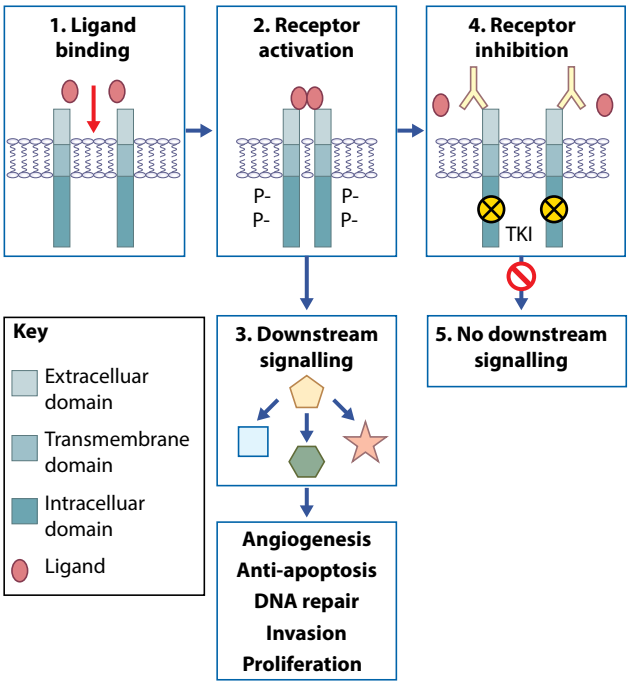

Figure 30.2 Growth factor independence can lead to sustained signalling in pathways that control essential biological functions, such as growth, apoptosis, angiogenesis, invasion and DNA damage repair. Ligand binding **(1)** leads to receptor dimerization and activation **(2)** through phosphorylation of tyrosine residues on the intracellular domain. Downstream signal transduction **(3)** activates important biological functions necessary for tumour growth, survival and spread. This process can be blocked **(4)** by monoclonal antibodies (MAB) that target the extracellular domain of the receptor or by small molecule tyrosine kinase inhibitors (TKI) that interact with enzymatic activity in the intracellular part of the receptor. These inhibitors are able to switch off downstream signalling events **(5)**.

c-erbB receptors are attractive therapeutic targets in SCCHN. Two classes of drugs, MAB and small molecule tyrosine kinase inhibitors (smTKI) have entered clinical trials. MAB are directed against the extracellular domain of the receptor, while smTKI inhibit the intracellular kinase domain of the receptor.

ANTI-EGFR MAB

Anti-EGFR MAB in the curative setting

A number of EGFR-targeted MAB have been tested in the clinic. They differ in terms of their species of origin (murine, chimeric (part human/part murine) or fully human) and the part (epitope) of the EGFR protein that they target. Cetuximab (C225, Erbitux) is a human-murine chimeric MAB. *In vitro* studies showed antitumour activity through anti-proliferative effects, direct cytotoxicity and potentiation of the effects of chemotherapy or radiotherapy.[15–18] In addition, *in vivo* experiments

demonstrated anti-angiogenic effects.[19] Early stage clinical trials confirmed the efficacy of cetuximab in combination with chemotherapy or radiotherapy.[20–24]

In a phase III study of 424 subjects with locally or regionally advanced SCCHN, locoregional control (median 24.4 vs. 14.9 months; hazard ratio: 0.68; P = 0.005) and overall survival (median 49.0 vs. 29.3 months; hazard ratio: 0.74; P = 0.03) were significantly prolonged in patients receiving radiotherapy and cetuximab compared to those treated with radiotherapy alone.[25] Cetuximab was associated with a higher incidence of rash and infusion reactions, but otherwise the grade 3 and greater toxic effects were the same in the 2 groups. Further analysis of the data showed that the occurrence of skin reaction represented a biomarker of favourable outcome in this group of patients.[26] The clinical importance of these findings, especially in an era in which concomitant chemoradiotherapy (not radiotherapy alone) is the standard-of-care, has been questioned. As a result, the Radiation Therapy Oncology Group (RTOG) conducted a follow-on study (RTOG-0522) in 940 patients with locoregionally advanced disease in which they tested radiation plus cisplatin versus radiation, cisplatin and cetuximab. Disappointingly, there were no significant differences in 2-year progression-free or overall survival rates.[27] The triple combination of bio-chemoradiotherapy was associated with significantly worse grade 3 and 4 mucosal/skin reactions. In a different approach, the phase II TREMPLIN study randomly assigned patients with locally-advanced laryngo-hypopharyngeal cancers, who had had a > 50% response to induction taxane-based triplet chemotherapy, to either concomitant cisplatin-based chemoradiotherapy or cetuximab-RT.[28] Of 153 patients who enrolled in the study, 116 were randomized after induction chemotherapy (i.e. they had a sufficiently good response to treatment). There were no differences in outcomes between the two treatment groups in terms of larynx preservation or overall survival.

Similar findings have been reported with a human MAB, zalutumumab, from the DAHANCA-19 study in which 619 patients were enrolled to receive modestly accelerated radiotherapy, the hypoxic cell sensitizer nimorazole and cisplatin (if indicated), with or without zalutumumab.[29] The majority of patients had stage III/IV disease and 70% received concomitant cisplatin. Treatment was well tolerated, but almost all (94%) patients in the zalutumumab arm reported a skin rash (grade 3–4 in 29%). No difference was seen between the study arms in terms of locoregional control at 3 years (78% in the zalutumumab arm and 79% in the control arm, (hazard ratio 0.8; 95% confidence interval 0.6–1.2). The data for disease-free and overall survival rates also failed to show a difference between the zalutumumab and control arms.

In addition, two studies with panitumumab (Vectibix), a fully human anti-EGFR monoclonal antibody have yielded negative data.[30, 31] The CONCERT-1 study randomized patients with previously untreated stage III-IVb disease to chemoradiotherapy or chemoradiotherapy plus panitumumab.[30] Of the 150 patients treated, 63 received standard chemoradiotherapy and 87 received chemoradiotherapy plus panitumumab. Locoregional control (LRC) at 2 years was non-statistically significantly better for standard chemoradiotherapy (68% vs. 61%) and the overall comparison for LRC showed a hazard ratio of 1.33 (95% confidence intervals (95% CI) 0.77–2.30). Data for progression-free and overall survival also showed no benefit from the addition of panitumumab (hazard ratios 1.15 (95% CI 0.68–1.96) and 1.63 (95% CI 0.88–3.02), respectively). The combination with panitumumab was significantly more toxic, with increased grade ≥ 3 dysphagia (40% vs. 27%), grade ≥ 3 mucosal inflammation (55% vs. 24%) and grade ≥ 3 radiodermatitis (31% vs. 13%). The CONCERT-2 study had a different design and evaluated platin-based chemoradiotherapy vs. radiation plus panitumumab (without platin chemotherapy) in patients with unresected stage III–IVb disease.[31] Of the 151 patients treated, 61 received standard chemoradiotherapy and 90 received radiation plus panitumumab. As with CONCERT-1, there was a non-statistically significant difference in LRC with radiation plus panitumumab performing worse (hazard ratio 1.61 95% CI 0.98–2.66), p = 0.06). A similar trend was also seen in terms of overall survival (hazard ratio 1.59 95% CI 0.91–2.79). Radiation plus panitumumab showed a statistically significant detriment for progression-free survival in this study (hazard ratio 1.73 (95% CI 1.07–2.81). Again, grade ≥ 3 radiation-induced toxicities were more common in the patients who received panitumumab.

Taken together, these data indicate that, in the curative setting, anti-EGFR MAB therapy should be restricted to the use of cetuximab plus radiotherapy. The precise indications for how this should be used, to replace cisplatin in patients who will not tolerate standard chemoradiotherapy or as a less toxic treatment in human papillomavirus positive oropharyngeal cancers (HPV+ OPC), remains to be defined precisely. In the latter case, a number of studies are ongoing to define the role of cetuximab plus radiotherapy combinations in HPV+ OPC [RTOG 1016 NCT01302834, UK De-Escalate HPV NCT01874171 and Trans-Tasman Oncology Group NCT01855451].

Anti-EGFR MAB in the palliative setting

Cetuximab has also been shown to improve the outcome of first-line palliative chemotherapy. In the EXTREME study, 442 eligible patients with untreated recurrent/metastatic SCCHN received cisplatin (100 mg/m^2) or carboplatin (area under the curve of 5 mg/mL/min) plus 5-fluorouracil (1 g/m^2 per day for 4 days) every 3 weeks for a maximum of 6 cycles. Cetuximab (400 mg/m^2 loading dose, then 250 mg/m^2 per week) was administered to 222 randomly selected patients. Patients in the cetuximab arm who showed stable disease were permitted to continue with maintenance cetuximab until disease progression or unacceptable toxicity. This study showed that the cetuximab/platinum/5-fluorouracil combination prolonged median overall survival from 7.4 months to 10.1 months (P = 0.04). There were also increases in the median progression-free survival time (3.3 to 5.6 months; P < 0.001) and the response rate (20% to 36%; P < 0.001).[32]

A similar trial design was employed for the SPECTRUM study, which evaluated the humanized MAB panitumumab. Patients in both groups received up to six 3-weekly cycles of intravenous cisplatin (100 mg/m^2) and 5-fluorouracil (1 g/m^2 per day for 4 days), while those in the experimental group also received intravenous panitumumab.[33] As in the EXTREME trial, patients randomized to panitumumab could continue maintenance MAB treatment. A total of 657 patients were randomized and the median overall survivals were 11·1 versus 9.0 months (hazard ratio 0·873; P = 0·1403) in the panitumumab and control groups, respectively. Despite this negative finding for overall survival, there was a statistically significant improvement in median progression-free survival in favour of panitumumab (5.8 vs. 4.6 months, hazard ratio 0·780; P = 0·0036). In sub-group analysis, the median overall survival in patients with p16-negative, but not p16-positive, tumours was prolonged in the panitumumab group (11.7 vs. 8.6 months; hazard ratio 0·73; P = 0·012). A number of toxicities, including rash and biochemical abnormalities were more common in the MAB-treated group.

Single-agent zalutumumab has been assessed in a 2:1 randomized phase III study versus best supportive care (including methotrexate) in 286 patients with platinum-resistant SCCHN.[34] The median overall survivals in the zalutumumab and control groups were 6.7 and 5.2 months (hazard ratio 0.77; P = 0.065), respectively. There was a statistically significant improvement in progression-free survival for zalutumumab (hazard ratio 0.63; P = 0.0012). As for previous studies, rash was more common in the group randomized to the anti-EGFR MAB.

Therefore, it appears that triple-agent therapy with platin/5-fluorouracil and cetuximab may be beneficial for patients as first-line therapy for relapsed/metastatic disease. In practice, many patients do not receive the triple therapy because of concerns about the additional toxicity of adding cetuximab to standard treatment. Although single-agent cetuximab is licensed for use in the USA, its use is not approved in Europe. Other single agent anti-EGFR MABs should not be used in relapsed/metastatic head and neck cancers.

SMALL MOLECULE TYROSINE KINASE INHIBITORS

Small molecule tyrosine kinase inhibitors in the curative setting

Gefitinib (ZD1839, Iressa) is a low-molecular weight smTKI that is highly specific for EGFR. By competing with ATP on the intracellular domain of EGFR it has been shown to prevent receptor autophosphorylation with resultant anti-proliferative effects observed in a variety of human xenograft models. Furthermore, combining gefitinib with cytotoxic chemotherapy increases growth inhibition and apoptotic cell death.[35–37]

It has been reported that gefitinib can be safely combined with chemoradiotherapy both with standard cisplatin-based chemoradiotherapy and with a rather unconventional split-course, twice-daily schedule with 5-fluorouracil and hydroxyurea.[38, 39] Results for erlotinib in this context have been disappointing with no improvement in treatment outcomes and increased toxicity when combined with chemoradiotherapy in a randomized phase II study.[40]

Lapatinib is an oral dual smTKI with action against both EGFR and c-erbB2/(HER-2).[41] It has demonstrated activity both *in vitro* and *in vivo*, as well as showing tolerability in phase I clinical trials.[42] A placebo-controlled randomized window-of-opportunity biomarker study has been performed with this agent in patients with advanced SCCHN. A single agent response rate of 17% was reported, with biomarker evidence of significantly reduced proliferation and receptor phosphorylation in the lapatinib treated group.[43] A phase I dose escalation study of lapatinib administered during radical chemoradiotherapy has been completed in patients with stage III and IV head and neck cancer.[44] Patients were enrolled in three cohorts of escalating lapatinib dose: 500 mg, 1000 mg and 1500 mg/day. Patients received one week of lapatinib alone followed by 6.5 to 7 weeks of the same dose of lapatinib plus radiotherapy 66–70 Gy and cisplatin 100 mg/m^2 on days 1, 22 and 43 of radiotherapy. The most common Grade 3–4 adverse events were radiation mucositis, radiation dermatitis, lymphopaenia and neutropaenia. The recommended phase II dose was defined as lapatinib 1500 mg/day with chemoradiation. Based on these findings, randomized phase II and III studies of lapatinib plus chemoradiation were initiated.

The randomized phase II study assessed the activity and safety of concurrent chemoradiotherapy and lapatinib followed by maintenance treatment in locally advanced, unresected stage III/IVA/IVB head and neck cancer.[45] Patients were randomized 1:1 to concurrent chemoradiotherapy and placebo followed by placebo or concurrent chemoradiotherapy and lapatinib followed by lapatinib. Treatment continued until disease progression or study withdrawal. Primary endpoint was complete response rate by independent review 6 months post-chemoradiotherapy. Sixty-seven patients (median age 56 years; 97% Eastern Cooperative Oncology Group performance status ≤1; 82% stage IV) were recruited. Lapatinib combined with chemoradiation was well-tolerated. Grade 3/4 toxicities during CRT were balanced between arms, with the exception of an excess of grade 3 diarrhoea (6% vs. 0%) and rash (9% vs. 3%) and two grade 4 cardiac events in the lapatinib arm. Complete response rate at 6 months post-chemoradiotherapy was 53% with lapatinib versus 36% with placebo in the intent-to-treat population. The progression-free survival and overall survival rates at 18 months were 55% vs. 41% and 68% vs. 57% for the lapatinib and placebo arms, respectively. The difference between study arms was greatest in p16-negative disease (median progression-free survival >20.4 months [lapatinib] vs. 10.9 [placebo]). These data led to the instigation of the randomized phase II TRYHARD study (NCT01711658) in patients with HPV-ve disease.

A randomized phase III study of lapatinib administered concomitantly with chemoradiotherapy and as maintenance monotherapy in patients with high-risk surgically-treated SCCHN has also been reported.[46] Patients with

resected stage II-IVA SCCHN, with a surgical margin ≤ 5 mm and/or extracapsular extension in metastatic cervical nodal disease were randomized to chemoradiotherapy (66 Gy total dose and 100 mg/m^2 cisplatin administered on days 1, 22 and 43) plus placebo or lapatinib (1500 mg/day) prior to and during chemoradiotherapy, followed by 12 months of maintenance monotherapy (either placebo or lapatinib). Six hundred and eighty-eight patients were enrolled; 346 received lapatinib and 342 received placebo. With a median follow-up of 35.3 months, the study was terminated early due to the apparent plateauing of disease-free survival events. Median disease-free survival was 53.6 months and not reached for lapatinib and placebo, respectively; hazard ratio 1.10 (95% CI 0.85–1.43). No significant differences in disease-free survival by HPV status, or overall survival, were observed between the two treatment arms. Similar numbers of patients in both treatment arms experienced adverse events, with more patients in the lapatinib arm experiencing serious events (48% vs. 40%). This study demonstrated that adding lapatinib to chemoradiotherapy and its use as long-term maintenance therapy did not offer any efficacy or safety benefits compared with placebo, in patients with surgically-treated high-risk SCCHN.

Afatinib is an irreversible inhibitor of EGFR, c-erbB2/HER2 and c-erbB4/HER4 that is being investigated in a number of settings in SCCHN. In the primary treatment setting, it is being tested in combination with chemoradiation (NCT01732640), and as adjuvant therapy after definitive chemoradiation in high-risk patients (phase III LUX2 study NCT01345669) or after surgery (GORTEC 2010-02, EudraCT 2010-023265-22). As yet, data are not available to permit a judgement of the potential role of this agent in the curative setting in patients with SCCHN.

Overall, despite significant clinical trial activity, there is no clear indication for the use of a smTKI in the treatment of newly diagnosed SCCHN. This is most clearly true in the case of combinations of smTKI with definitive chemoradiotherapy, but the existing data also suggest that there is no clear role in the adjuvant setting. Further trial data will become available in the coming years and this situation may change.

Small molecule tyrosine kinase inhibitors in the palliative setting

Gefitinib was evaluated in phase I trials that included a number of patients with head and neck cancer.[47–50] It was well-tolerated at doses from 150 to 800 mg/m^2, the most frequent grade 1 or 2 toxicities were diarrhoea (47–55%), asthenia (44%) and an acneiform follicular rash (46–64%). Antitumour activity, including both partial responses and cases of prolonged stable disease, was observed at all doses. Clinically meaningful stable disease was achieved in 50% of patients with SCCHN, and quality-of-life ratings also remained stable during treatment, except in one study where they improved significantly over time.[50]

A phase II study has evaluated oral gefitinib (500 mg/day) as first- or second-line monotherapy in 52 patients with recurrent or metastatic SCCHN most of whom had previously received combination chemotherapy or radiotherapy.[51] Forty-seven patients were evaluable for tumour response and an objective partial response rate of 10.6% (one complete response) was demonstrated. Disease control, defined as objective tumour response plus stable disease, was achieved in 53% of patients and was sustained for more than 6 months in 13% of patients. The response rates and survival times of patients who received gefitinib as first-line therapy were not significantly different to those of patients who had received prior chemotherapy. Overall, the median times to progression and death were 3.4 months and 8.1 months respectively, with an estimated 1-year survival of 29%. There was only a single case of grade 4 toxicity (hypercalcaemia), a 4–6% incidence of grade 3 toxicity (anorexia, diarrhoea, nausea and hypercalcaemia), grade 1 or 2 skin rash in 48% and grade 1 or 2 diarrhoea in 50%. A second study using single-agent gefitinib at a dose of 500 mg/day has also been reported.[52] Clinical, symptomatic and radiological response, time to progression, survival and toxicity were recorded. Forty-seven patients were treated and the observed clinical response rate was 8% with a disease control rate (complete response, partial response, stable disease) of 36%. Thirty-four percent of patients experienced a symptomatic improvement. The median time to progression and survival were 2.6 and 4.3 months, respectively. Acneiform folliculitis was the most frequent toxicity observed (76%) but the majority of cases were grade 1 or 2. Only 4 patients experienced grade 3 toxicity of any type (all cases of folliculitis). The 250 mg/day dose was also tested in phase II trial and appeared to be less active than the 500 mg/day dose.[53]

Subsequently, a randomized phase III study was conducted to compare survival in patients with recurrent or metastatic SCCHN treated with gefitinib 250 or 500 mg/day or standard-of-care single-agent methotrexate.[54] Four hundred and eighty-six patients were randomized to oral gefitinib 250 mg/day, gefitinib 500 mg/day, or intravenous methotrexate 40 mg/m^2 weekly. Neither of the gefitinib doses improved overall survival compared with methotrexate (hazard ratios 1.22 (95% CI, 0.95–1.57 and 1.12 (95% CI, 0.87–1.43), respectively. The median overall survivals were 5.6, 6.0, and 6.7 months for gefitinib 250 mg/day, gefitinib 500 mg/day, and intravenous methotrexate, respectively. Interestingly, gefitinib therapy appeared to be associated with an increased risk of haemorrhagic events. These data do not support the use of gefitinib as a palliative therapy in relapsed/metastatic SCCHN.

Afatinib has been assessed in the phase III LUX head and neck-1 study in patients receiving second-line therapy for relapsed/metastatic SCCHN.[55] A total of 583 patients were treated with afatinib (322 patients) or methotrexate (161 patients). Afatinib significantly increased median progression-free survival (2.6 vs. 1.7 months, p = 0.03) but did not improve median overall survival (6.8 vs 6.0 months) relative to methotrexate. The overall response rates of the two study arms were low – 10.2% and 5.6%, respectively. In an integrated analysis of quality of life, afatinib showed a delay in deterioration of global health status, pain and

swallowing problems (all $p \leq 0.03$). The profile of toxicities was markedly different between the two treatments, with afatinib causing more rash and diarrhoea and methotrexate causing more stomatitis and leukopenia. A randomized phase II comparison of afatinib and cetuximab has also demonstrated that afatinib has similar antitumour activity to cetuximab, as assessed by tumour shrinkage on treatment.[56] It remains to be seen if, on the basis of these data, afatinib finds a place in the treatment process for patients with relapsed/metastatic SCCHN.

Molecularly targeted radiosensitizers

Radiotherapy is an extremely effective therapy for SCCHN. Sophisticated modern 3-dimensional conformal planning techniques allow us to target tumour volumes more accurately than was the case with previous conventional methods. In addition, advanced delivery systems, such as intensity-modulated radiotherapy (IMRT) and image-guided radiotherapy (IGRT), offer the prospect of higher rates of tumour control with reduced toxicity.

In tandem with the development of advanced radiotherapy techniques, a parallel track of preclinical and clinical studies has evaluated combinations of radiotherapy with cytotoxic drugs in an attempt to enhance radiation-induced cytotoxicity in cancer cells.[57] As a result of meta-analyses of a large number of small- to medium-sized randomized trials, we now recognize radiotherapy delivered with concomitant platin monotherapy as the standard-of-care for locally advanced SCCHN.[58]

As discussed earlier, there is an increasing understanding of the molecular pathways leading to malignant transformation in normal cells. DNA damage, which is an inevitable consequence of cellular metabolism and proliferation, can also be caused by exogenous agents including ionizing and non-ionizing irradiation and environmental chemical toxins. Clinical and medical oncologists exploit these agents, in the form of radiotherapy and chemotherapy, to inflict DNA damage on cancer cells. However, cancers frequently have a deranged DNA damage response and, as discussed earlier, this leads to a state of genomic instability that can drive the evolution of more aggressive cellular clones within the tumour. Importantly, the loss of key components of the DNA damage response may also constitute a cancer-specific molecular 'Achilles' heel' that is vulnerable to therapeutic exploitation with a new generation of targeted radiosensitizing agents.[59] Development of radiosensitizers designed to target the DNA damage response (DDR) will require very careful clinical trial design, because of the potential risks of unwanted and unacceptable normal tissue toxicity arising from damage to normal cells.[57, 59]

CELL CYCLE CONTROL AND DNA DAMAGE REPAIR

Cell division is an essential component of development, growth and tissue repair. Since this process involves replicating the cell's genetic material, it is not surprising that it is tightly regulated to ensure that each daughter cell receives an accurate copy of the genome. Failure to copy the cellular DNA faithfully exposes the daughter cells to the risk of inheriting mutations. During the cell cycle, there are opportunities for the cell to slow down or pause while it assesses genomic integrity and corrects errors in the sequence of DNA. Cells can also slow down or stop in the cell cycle when they experience DNA damage, including that inflicted by radiotherapy and/or chemotherapy. Overall, there are 4 cell cycle checkpoints: at the G1/S transition, during S phase, early in G2 phase and late in G2 phase. Two of these are particularly relevant to the cellular response to radiotherapy. The G1/S checkpoint allows diploid (2n, 46 chromosomes) cells to pause before entering synthesis (S) phase, during which the entire DNA complement is duplicated to create a cell with 4n DNA content before mitosis. The TSGs *TP53* and retinoblastoma (*RB1*) play central roles in the G1/S checkpoint. *TP53* pathway mutation or inactivation is extremely common in many tumours, including head and neck cancers. In fact, smoking-induced SCCHN demonstrates almost universal loss-of-function mutations of the p53 pathway, with 84% of tumours showing *TP53* mutation in The Cancer Genome Atlas Network analysis.[4] In contrast, only 3% of HPV-positive SCCHN showed mutations of *TP53*, but these tumours inactivate the pathway through interactions between viral E6 and E7 proteins with p53 and Rb proteins, respectively.[4] As a result of this very frequent aberrant status of the G1/S checkpoint, most SCCHN have become highly reliant on a functional G2/M checkpoint.

Ionizing radiation induces a number of lesions in DNA, ranging from purine and pyrimidine lesions to single-strand (SSB) and double-strand breaks (DSB) in the DNA. DSB are potentially the most lethal DNA lesions induced by radiotherapy and therapies that can prevent their repair/resolution have the potential to be profoundly radiosensitizing. As might be expected, there are specific mechanisms to detect and repair radiation-induced abnormalities in DNA structure: DSBs are repaired by non-homologous end-joining (NHEJ) repair during G1 phase of the cell cycle and by high-fidelity homologous recombination (HR) in S and G2 phases; SSBs and base damage are repaired through the base excision repair pathway.[60]

Different types of radiation-induced DNA damage are sensed by mechanisms that activate specific DDR kinases: ataxia telangiectasia mutated (ATM) and ataxia telangiectasia and Rad3-related (ATR), which phosphorylate the checkpoint kinases, Chk1 and Chk2. In turn, these proteins transfer the signal to different effector molecules. The specific pathways involved are illustrated in **Figure 30.3**.

RADIATION-INDUCED CELL DEATH AND SYNTHETIC LETHALITY

Radiation-induced cell death requires cells to attempt to divide with unrepaired, damaged DNA. This is thought to result in cell death through mitotic catastrophe, in which a cell is unable to complete mitosis successfully and dies in the process.[61, 62] Alternatively, radiation can induce a state of replicative senescence in which the cell permanently loses

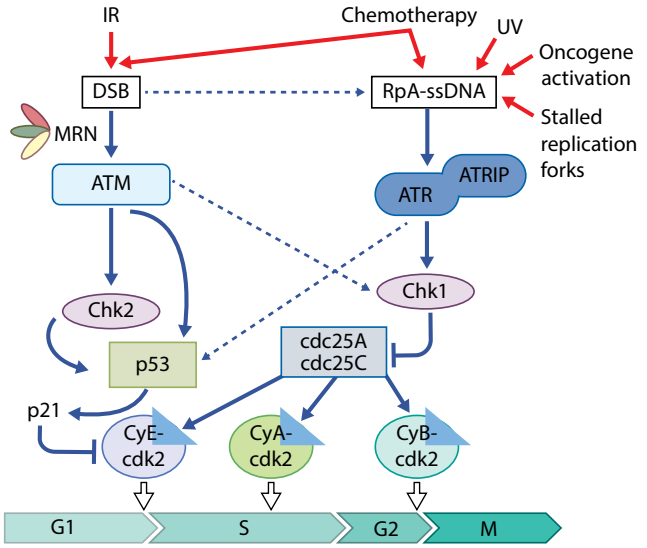

Figure 30.3 Schematic representation of the DNA damage response. The ATM pathway is activated strongly by DNA double-stranded breaks (DSB), causing activation of Chk2 and p53 with subsequent G1 cell cycle arrest. Diverse inputs converging on RpA-coated single-stranded DNA (ssDNA) activate the ATR-ATRIP complex, with downstream phosphorylation of Chk1, amongst other targets, resulting in G2/M arrest. The ATR pathway also plays an important role in S-phase progression and replication fork stabilisation. There is evidence of substantial crosstalk between these pathways (indicated by the dotted arrows).

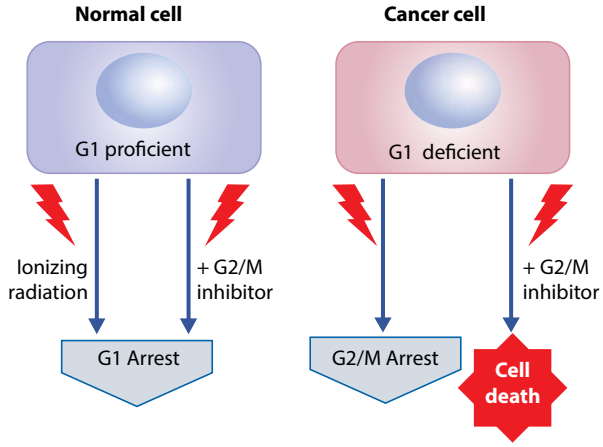

Figure 30.4 G1 checkpoint-deficient cancer cells rely heavily on radiation-induced G2/M arrest to survive after irradiation. Inhibiting the G2/M checkpoint in cancer cells will abrogate all checkpoint function in cancer cells, while intact G1 checkpoint arrest allows DNA repair in normal cells. This synthetically lethal interaction underpins interest in the G2/M checkpoint as a target for radiation-drug combination therapies.

the ability to divide and, thus, becomes non-clonogenic (and, therefore, no longer a threat to the host).[63] As discussed above, the majority of SCCHN (both HPV-ve and HPV+ve) lack a normal p53-mediated G1/S checkpoint and are highly dependent on the ATR-Chk1 pathway to mediate S and G2/M arrest to allow repair of DNA damage following irradiation. Thus, G2/M checkpoint control has been viewed as a particularly attractive target for cancer-specific radiosensitization.[59] Irradiated cancer cells that are defective in p53 pathway signalling will be unable to stop at the G1/S checkpoint and will be highly vulnerable to drugs that inhibit the G2 checkpoint.[64] Such cancer cells will proceed into mitosis before they have been able to repair their radiation-induced DNA damage and, as a result, will run a significant risk of mitotic catastrophe and cell death. This activity of G2/M checkpoint inhibitors in p53-defective tumour cells is an example of a so-called "synthetic lethal interaction" with ionizing radiation and represents a promising prospect for developing cancer-selective radiosensitizing drugs (**Figure 30.4**).

TARGETED DRUGS AS RADIOSENSITIZERS

ATR inhibitors

ATR inhibitors can radiosensitize cancer cells through disruption of the intra-S and G2 checkpoints and, perhaps, by disrupting ATR's roles in the DSB response, replication fork stabilization and the cellular response to hypoxia.[65,66] Small molecule inhibitors of ATR kinase have been tested in preclinical studies in combination with genotoxic chemotherapy or ionizing radiation. Thus far, there have been no publications on ATR inhibitors in patients with cancer, although early phase clinical trials have been initiated.

VE-821 (Vertex Pharmaceuticals, UK) is the most extensively studied ATR inhibitor to date. It caused cell death and growth inhibition in cancer cell lines and synergized with DNA-damaging agents, such as ionizing radiation.[67] The role of p53 pathway function in determining cellular sensitivity to VE-821 is, as yet, unclear.[65] A related molecule, VE-822 (Vertex Pharmaceuticals, UK) sensitized pancreatic cancer cell lines to both radiation and gemcitabine *in vitro*, without significant toxicity in normal cell lines. It also demonstrated efficacy in pancreatic tumour xenografts, with inhibition of radiation-induced Chk1 phosphorylation and a reduction in tumour growth when combined with radiation or gemcitabine-based chemoradiation in comparison to untreated or single-agent treated controls. Importantly, VE-822 did not cause any additional in-field gastrointestinal radiation-induced toxicity in animal models.[68] Specific studies in head and neck cancer models are not yet available, but it is reasonable to hypothesize that the data generated thus far should be relevant in the context of SCCHN.

AZD6738 (AstraZeneca plc) is a potent ATR inhibitor which can inhibit Chk1 pathway signalling.[69] The agent caused dose- and time-dependent induction of replication stress (measured by S-phase cell cycle accumulation by flow cytometry), increased DNA-strand breaks formation (measured by γH2AX focus formation) and growth inhibition/cell death *in vitro*. When combined with ionizing radiation *in vitro*, AZD6738 showed significant enhancement of growth inhibition activity compared to radiation or drug treatment alone in head and neck cancer (and other) cell lines. AZD6738 is currently being tested in phase I clinical trials, both as monotherapy and combined with either radiotherapy or chemotherapy [NCT02223923, NCT02264678].

Chk1 inhibitors

Chk1 is directly downstream of ATR in the DNA damage response signalling cascade and is phosphorylated by it. A number of Chk1 inhibitors have been tested preclinically,[70] but few have entered clinical trials. UCN-01 showed enhancement of radiation and genotoxic chemotherapy-induced cytotoxicity that was selective for p53-dysfunctional cells.[71] It was tested in phase I trials as monotherapy[72] and in combination with DNA-damaging agents such as platinum,[73] topoisomerase inhibitors[74] and nucleoside analogues.[75, 76] In phase II studies, UCN-01 was tested combined with DNA-damaging chemotherapy but its development was aborted due to lack of clinical efficacy.[77–79]

AZD7762 is a combined Chk1 and Chk2 inhibitor which radiosensitized tumour cells *in vitro* and *in vivo* in preclinical trials. Although it was initially suggested that this activity was p53-dependent, these data were not entirely clear-cut.[80, 81] In pancreatic cancer cell lines *in vitro* and in xenografts, AZD7762 sensitized to radiation alone and radiation in combination with gemcitabine, with abrogation of the radiation-induced G2/M checkpoint and inhibition of HR repair.[82] AZD7762 was tested in a clinical trial as a single-agent and in combination with gemcitabine (NCT00413686). Unfortunately, its development was terminated prematurely because of concerns about toxicity (especially cardiovascular effects which were manifest as significant reductions in cardiac ejection fraction).[83]

Other Chk1 inhibitors have been developed, including PF-00477736,[84, 85] MK8776 (otherwise known as SCH900776)[86] and SAR-020106.[87] The latter agent, SAR-020106, was shown to be a potent radiosensitizer both in *in vitro* and *in vivo* models. The drug inhibited radiation-induced G2/M arrest and reduced clonogenic survival in p53-deficient, but not p53-competent, tumour cells. Importantly, SAR-020106 promoted mitotic entry after irradiation in all cell lines: p53-deficient cells were likely to undergo apoptosis or become aneuploid, while p53 wild-type cells experienced a post-mitotic G1 arrest followed by subsequent normal cell cycle re-entry. Following combined treatment with SAR-020106 and radiation, HR-mediated DNA damage repair was inhibited in all cell lines. However, a significant increase in pan-γH2AX-stained apoptotic cells was observed only in p53-deficient cell lines. Efficacy was confirmed *in vivo* in a clinically relevant human head and neck cancer xenograft model.[87] The lack of oral bioavailability of this agent has arrested its clinical development. However, an orally bioavailable Chk1 inhibitor (CCT245737)[88] is entering clinical studies in a range of solid cancers and it is hoped that its development will include combination studies with radiation in disease subtypes that will include head and neck cancers.

Other G2/M-targeted checkpoint inhibitors

The Wee1 kinase regulates entry into mitosis, by negatively controlling CDK1 and 2. In a similar fashion to ATR and Chk1, it is active during normal unperturbed cell division, playing a role in the maintenance of genome integrity. A Wee1 kinase inhibitor (AZD-1775, formerly MK-1775) has been shown to sensitize p53-deficient tumour cell lines to radiation, with abrogation of radiation-induced G2 arrest and premature entry into mitosis.[89] The drug has also been shown to potentiate DNA-damaging agents *in vitro* and *in vivo*,[90, 91] and has reached a number of phase I trials. Cdc25 phosphatase is another G2 checkpoint target[92] and inhibitors have been developed that have shown activity against tumour cells and xenografts.[93]

Targeted immunomodulation as an anticancer strategy

In recent years, after decades of negative studies and false hopes, immunotherapy has emerged as a major new modality in the treatment of many solid cancers.[94] This change in the fortunes of immunotherapy has been underpinned by huge advances in our understanding of the fundamental biological principles that guide the activity of the immune system. In particular, a number of specific immune checkpoints have been discovered that are integral components of normal immune responses. In normal health, these checkpoints function to inhibit T-cells and prevent them from becoming chronically activated or aberrantly targeted against normal tissues. Effectively, they function as negative regulators or 'brakes' on the normal immune response. Many cancers subvert these inhibitory pathways in order to break free from immunosurveillance. Therefore, by activating brakes on the immune system, cancer cells are able to emerge from elimination/equilibrium phase and escape from immune detection and/or immune-related attack.[9]

Proteins that are expressed on activated T-cells, such as cytotoxic T-lymphocyte-associated protein 4 (CTLA4) and programmed death 1 (PD1), are key players that allow many cancers to evade anti-tumour immunity by interfering with the activation and effector phases of immune responses, respectively. CTLA4 is an important control mechanism that influences the activation phase of the immune response. As shown in **Figure 30.5**, when a specific tumour-associated antigen is presented by an antigen-presenting cell (APC) to a T-cell that expresses a T-cell receptor capable of recognizing it, there are two possible outcomes. In the first case, if the T-cell also receives a co-stimulatory signal via B7 on the APC binding to CD28 on the T-cell, the T-cell will become activated and capable of mediating an antitumour effect. However, in becoming activated, the T-cell upregulates CTLA4 on its surface and this is able to out-compete CD28 for binding of B7 on the APC. The net effect is that the T-cell can be switched off or anergized. Therapeutic MAB that target CTLA4 are able to block this negative interaction and enhance T-cell activation. In the effector phase of the immune

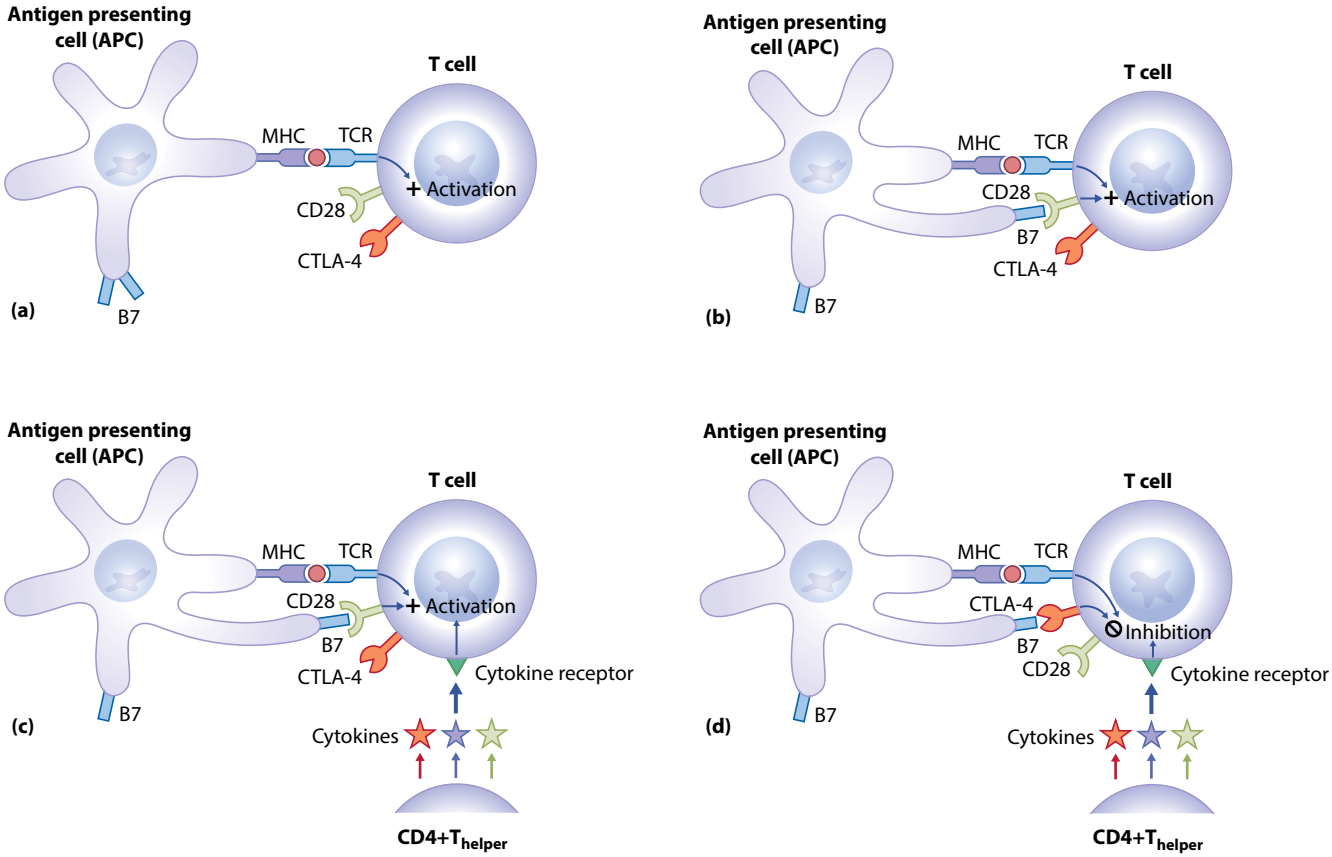

Figure 30.5 The activation phase of the immune response can be switched off by the T-cell protein CTLA-4. **(a)** Presentation of a tumour-associated antigen (TAA) on a major histocompatibility complex via a T-cell receptor leads to a positive signal (signal 1) to the T-cell; **(b)** To become fully activated, the T-cell must also receive a further signal (signal 2) when B7 on the APC binds to CD28 on the T-cell; **(c)** Activation is reinforced by cytokines released by CD4+ T_{helper} cells that bind to cytokine receptors on T-cells (signal 3); **(d)** Activation can be inhibited and the T-cell can be inactivated if CTLA-4 on the T-cell out-competes CD28 for binding of B7 on the APC (shutting off signal 2 and sending a negative message to the T-cell).

response (**Figure 30.6**), an activated T-cell can be prevented from engaging with and killing a tumour cell if the tumour cell expresses the negative regulatory ligand programmed death ligand 1 (PD-L1) on its surface (either constitutively or in response to interferon-gamma secreted by an activated T-cell). This negative interaction between T-cell and tumour cell can be interrupted by administration of specific MAB that block either PD-1 on the T-cell surface or PD-L1 on the tumour cell surface.

In addition to these two pathways, a large number of other checkpoints have been described at the immune checkpoint (e.g. TIM3, LAG3, OX40, GITR). Some of these checkpoints lead to inhibition and others to activation of immune responses. A large number of new therapeutic agents are currently in preclinical or clinical development and it is likely that some of these will reach the clinic in the next few years.

CLINICAL EXPERIENCE WITH CHECKPOINT INHIBITORS

Both anti-CTLA4 and anti-PD1/PD-L1 MAB have demonstrated significant activity in a range of non-SCCHN tumour types, including melanoma,[95–99] lung,[100] bladder[101] and mismatch repair-deficient bowel cancer.[102] Intriguingly, it appears that the likelihood of a patient deriving benefit from immunotherapy may correlate with the mutational burden and, hence, the neoantigenic load carried by their tumour.[103] This mutational load appears to be greatest in melanoma, but head and neck cancers (especially HPV-ve tumours) are also associated with a significant number of mutations.

In the context of SCCHN, there have been initial reports of single-agent activity in patients with relapsed/metastatic disease. The largest experience has accrued with single-agent therapy with the anti-PD1 monoclonal antibody, pembrolizumab. In the KEYNOTE-012 (NCT01848834) study, patients with PD-L1-positive (> 1% staining of tumour cells) tumours were divided into HPV+ve and HPV–ve cohorts and treated with 10 mg/kg of pembrolizumab every 2 weeks. Treatment beyond disease progression was permitted, as long as the patient was judged to be deriving clinical benefit from therapy. Overall, 26 of 51 patients had a reduction in tumour burden and 20% satisfied standard radiological criteria (RECIST v1.1) for response.[104] In a subsequent study, a larger group of 132 patients was treated with a fixed dose

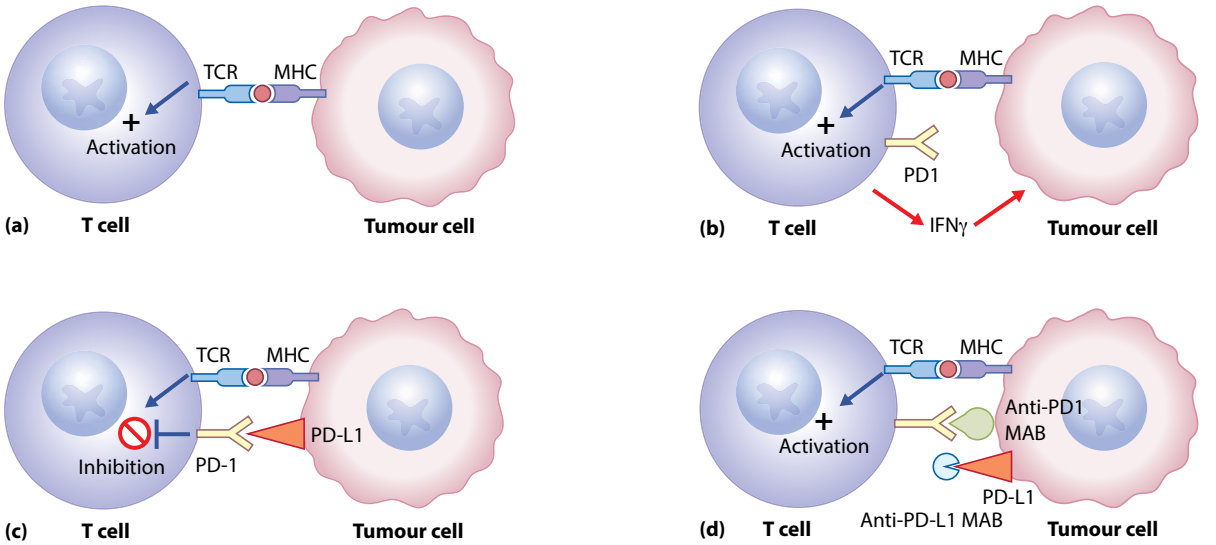

Figure 30.6 PD-1/PD-L1-mediated immune evasion by cancer can be reversed by immune checkpoint-inhibiting monoclonal antibody (MAB) therapy. **(a)** T-cells are frequently capable of recognizing tumour-associated antigens loaded on major histocompatibility (MHC) class I molecules. **(b)** In doing so, T-cells become activated and express programmed death 1 (PD-1) receptors on their surface and secrete interferon-γ (IFN-γ). **(c)** In response, tumour cells can upregulate expression of programmed death ligand 1 (PD-L1), which can bind to PD-1 on T-cells and switch them off. **(d)** Treatment with either anti-PD-1 or anti-PD-L1 MAB can block the interaction between PD-L1 on tumour cells and PD-1 on T-cells and as a result, anti-PD-1 or anti-PD-L1 MAB can reactivate T-cell activation against tumour cells.

of pembrolizumab (200 mg) every 3 weeks. Patients were included irrespective of PD-L1 status. The treatment was well tolerated with only 7.6% of patients experiencing a grade 3 or greater adverse effect. Of 99 patients who were evaluable for preliminary analysis, 18.2% showed a response (all partial responses) and 31.3% of patients had stable disease.[105] There are a number of ongoing randomized phase II and III clinical trials with both anti-PD1 and anti-PD-L1 agents (pembrolizumab [KEYNOTE-040 NCT02252042, KEYNOTE-048 NCT02358031], nivolumab [CHECKMATE-141 NCT02105636], durvalumab/MEDI4736 [HAWK NCT02207530, EAGLE NCT02369874] in patients with relapsed/metastatic disease that are likely to be reported in the next 2–3 years.

The clinical responses to immunotherapy tend to occur rather more slowly than with conventional cytotoxic chemotherapy and may be preceded by a period of disease progression – so-called pseudoprogression. In addition, the side effects of immune checkpoint inhibitors are entirely different from standard chemotherapeutic agents. In particular, by taking the brakes off the immune response, these agents are associated with significant auto-immune adverse reactions, such as skin rash, colitis, hepatitis and endocrinopathy (thyroid, adrenal and pituitary dysfunction). These effects appear to be more common with anti-CTLA4-targeted drugs rather than anti-PD1/anti-PD-L1 agents, but in all instances, require specialist management because they can evolve into serious, even life-threatening, conditions.

COMBINATIONS OF CHECKPOINT INHIBITORS AND RADIATION

There is evidence from both the laboratory and the clinic that radiation therapy can cause immunogenic cell death.[106–108] Furthermore, there are both preclinical and clinical data to demonstrate that immune checkpoint inhibition may enhance this effect and lead to systemic activity of a local therapy (e.g. radiation).[109, 110] These observations, combined with the excitement over single-agent activity of immune checkpoint inhibition, have led to a number of clinical studies that are combining immune checkpoint inhibitors with ionizing radiation. At present, there are no substantial reports of this approach in the literature, but it is likely that studies evaluating palliative hypofractionated radiotherapy and radical standard fractionation (with and without platin-based chemotherapy) will be reported in the coming years. This strategy certainly seems to hold promise, especially as a means of using intensive locoregional therapy as a means of generating systemic activity (and protection) against metastatic disease recurrence.

KEY POINTS

- An increasing understanding of the fundamental biological processes involved in cancer cell formation has resulted in the development and clinical use of drug strategies to treat head and neck cancer.
- Of note, Epidermal Growth Factor Receptor Inhibitors, Tyrosine Kinase Inhibitors, drugs which arrest cell cycle progression and sensitize cancer cells to the effects of radiotherapy have been used in various treatment regimens.
- Exciting improvements in treatment have resulted from the use of drugs which modulate the host immune system.

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CHAPTER 31

PROSTHETIC MANAGEMENT OF SURGICALLY ACQUIRED ORAL AND FACIAL DEFECTS

Chris Butterworth

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SEARCH STRATEGY

Data in this chapter may be updated by a Medline search using the keywords: maxillectomy, maxillary obturator, rhinectomy, facial prosthesis, dental assessment, dental implants, zygomatic implants and dental rehabilitation.

INTRODUCTION

This chapter deals with the planning and application of maxillofacial prosthodontic and prosthetic techniques for patients requiring prosthetic rehabilitation for surgical defects of the mouth and face. The text will primarily refer to the management of patients with oral, maxillary and mid-facial tumours.

Complex oral and facial rehabilitation aspects of treatment should be led by the maxillofacial prosthodontist in conjunction with the other core members of the multidisciplinary team (MDT) as well as additional extended members such as the dental hygienist and specialist dental/facial prosthetic technicians (See Chapter 97, A combined prosthetic and surgical approach). Where patients are dentate, ongoing liaison with the patient's primary dental care practitioner is also of utmost importance.

Osseointegrated implants are a very important tool in the management of complex oral and facial defects and the appropriate expertise should be available in the MDT to allow their application where clinically indicated either at the time of primary surgery or as part of definitive secondary rehabilitation. An appropriate funding stream for such treatment is also required due to the complexity and cost of these individual bespoke rehabilitative treatments.

Oral and facial rehabilitation treatment seeks to help address, or in many cases palliate, the patient suffering from the negative unwanted effects of surgical and oncological treatment modalities (**Box 31.1**).

BOX 31.1 Negative effects of treatment for H&N cancer

- Altered oral and facial anatomy
- Maxillary and facial defects
- Trismus
- Xerostomia
- Altered dental occlusion
- Bulky soft-tissue flaps
- Altered facial sensation
- Speech and swallowing problems

PRE-SURGICAL ASSESSMENT

All patients with oral, oro-pharyngeal, maxillary and mid-face tumours should be seen and assessed by the maxillofacial prosthodontist at an early stage in the patient journey, especially where there are good reasons to undertake early prosthetic rehabilitation. Dental pathology is extremely common in this group of patients and

appropriate dental management is required for the majority of patients.[1] All dentate patients should have a screening panoramic dental radiograph in conjunction with a detailed oral examination with appropriate decision making regarding dental extractions, restorations and definitive planning for prosthetic rehabilitation in terms of osseointegrated implant placement to support any definitive prosthesis that may be required.

Following a detailed assessment of the patient's dentition, a final decision regarding the definitive treatment plan should be made in the light of the patient's oral and general motivation, whilst taking into account the likely effects of the proposed oncological treatment strategy. Ideally, risk factors such as smoking and alcohol consumption should be addressed where they exist pre-treatment if complex rehabilitative treatments are to be considered. The overall proportion of head and neck cancer patients receiving osseointegrated implant treatment has been reported to be quite low.[2] Careful patient selection is required to ensure that the patient receives the appropriate benefit of the treatment especially where implants are placed primarily at the time of primary oncological surgery.

MANAGEMENT OF THE MAXILLECTOMY DEFECT

Prior to the advent of predictable free vascularized tissue transfer, the management of many maxillectomy defects was via prosthetic obturation. The use of prosthetic obturation has subsequently decreased considerably in modern surgical practice but still has a useful role in the management of patients who cannot receive complex autogenous reconstruction, where the access for subsequent surveillance is deemed to be an advantage or for small well-defined maxillary defects.

The use of a classification based approach to decision-making is a useful one and such classifications such as those by Brown[3] and Okay[4] are helpful in this respect. Brown's surgical-based classification has been widely adopted when considering the decision to reconstruct the maxilla and mid-face surgically whereas Okay's work is more directed to the maxillofacial prosthodontist and is very helpful in the design of maxillary obturator prostheses depending on the remaining dental configuration following surgery.

The decision-making process should be a joint one between the surgeon, the prosthodontist and the patient. It is clearly a multifactorial process and has to take into account the size and location of the tumour, the tumour subtype and histological features, the perceived prognosis for the patient and their fitness for surgery, their current dental status, mouth opening and desire for future dental rehabilitation.

In general terms, the more extensive maxillary defects should be surgically reconstructed with free tissue-transfer techniques. When the defect extends out of level 2,[3] the overall facial result tends to worsen and is more difficult to maintain with a prosthetic obturator (**Figure 31.1**). Defects involving the orbital floor should also ideally be reconstructed wherever possible to prevent the inferior displacement of the globe which results in a poor aesthetic facial appearance (**Figure 31.2**).

Preparation for a maxillectomy combined with prosthetic obturation must begin in advance of the operation with an outpatient visit with the maxillofacial prosthodontist. A clear and detailed surgical treatment plan should be provided to allow adequate planning and prescription for the surgical obturator prosthesis. Specifically, the planned alveolar margins of the resection in the dentate patient are very important to the accuracy of fit of the prosthesis at surgery (**Figure 31.3**). Dentate patients will always require pre-operative impressions for models and prosthesis construction whereas the edentulous patient may not, depending on whether they are currently wearing a well made and extended prosthesis. Often the surgical obturator prosthesis can be constructed with appropriate tooth replacement included but where there are significant time constraints prior to surgery or for the non-denture wearing edentate patient, a simple clear acrylic cover plate can

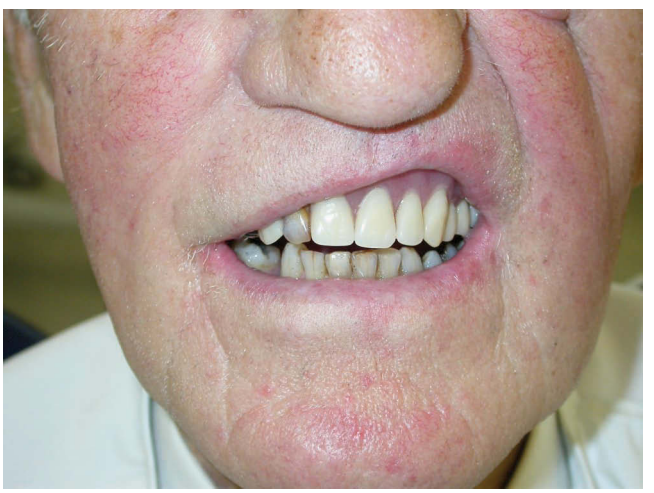


Figure 31.1 Lip contracture following level 2 maxillectomy and obturation.

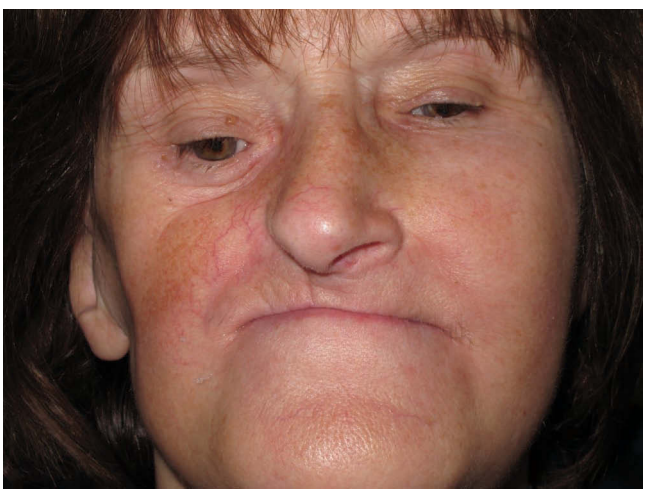


Figure 31.2 Significant drop in right globe position following maxillectomy involving the orbital floor.

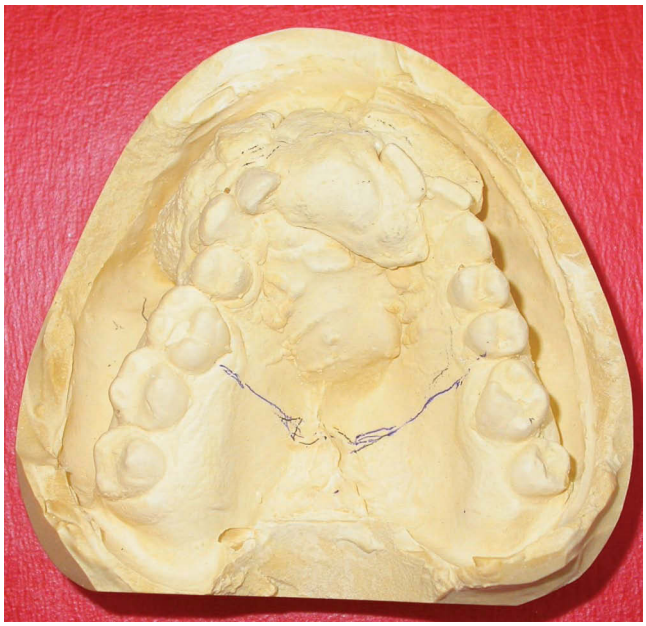


Figure 31.3 Marking the cast prior to maxillectomy.

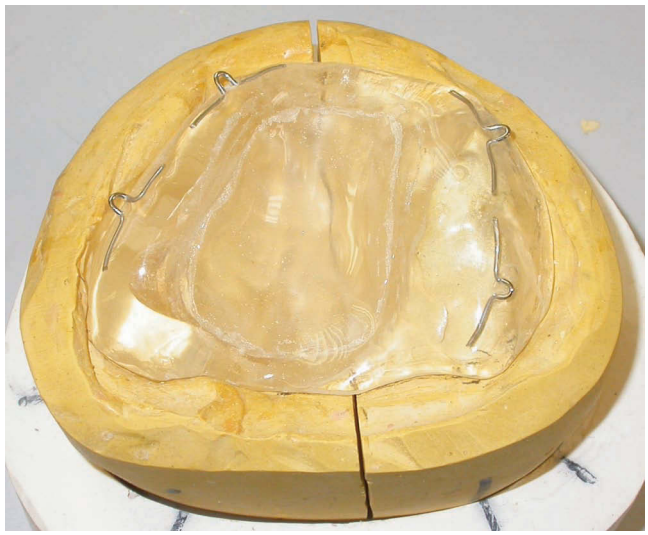


Figure 31.4 Surgical obturator with loops for circum-zygomatic wires.

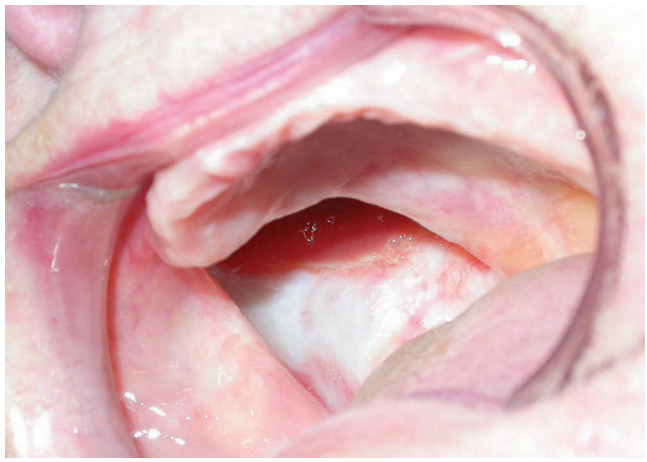


Figure 31.5 Healed split-skin graft in the cheek producing retentive scar band for obturator prosthesis.

be constructed. Depending on the size, extent and location of the proposed maxillectomy defect, the prosthesis should contain appropriate elements designed to assist with the retention of the appliance such as dental clasps or circum-zygomatic loops (**Figure 31.4**). Where ongoing retention difficulties are foreseen by the maxillofacial prosthodontist, specific plans for the concomitant insertion of osseointegrated implants at the time of surgery should be made.

A clear explanation of the various stages of treatment should be given to the patient, including the need for regular follow-up visits with the prosthodontist following surgery, together with what they should expect from the prosthetic obturator.

SURGICAL MODIFICATIONS TO FACILITATE OBTURATOR PROVISION

Where possible, bone cuts through the maxillary alveolus should be undertaken through an edentulous region or through the middle of a dental extraction socket following the removal of the required tooth to facilitate this. This ensures that any remaining abutment teeth have uncompromised periodontal bone support for the future which is so important in their ongoing role in supporting the obturator prosthesis.

The incisions through the hard palate mucosa should ideally be made laterally to the bone cuts to create a keratinized mucosal flap which folds over the cut edge of the palatal bone. This provides a cushioning effect for the future prosthesis which tends to move about this axis to some degree during masticatory function.

The cheek defect should be grafted with a carefully sutured split-skin graft. This results in the production of a scar band within the cheek which helps to retain the obturator prosthesis (**Figure 31.5**). This is essential where a conventional obturator is being provided and this is one of the few areas where retention can be gained. Its use is less important where other forms of retention such as osseointegrated implants are to be used to assist with prosthesis retention.

Where exposed into the resulting defect, the inferior turbinate(s) should be removed to provide more vertical space for the obturator elements of the prosthesis and to prevent future trauma. Once the resection has been completed, the surgical obturator prosthesis should be relined and fitted prior to extubation of the patient. A variety of materials have been advocated to obturate the surgical defect including black gutta percha, silicone putty impression material and foam-based products. The author favours the use of addition-cured silicone putty as it is readily available, easy to use and provides rigid support for the cheek as well as the ability to engage undercuts in the defect which can assist in the overall retention of the prosthesis in the immediate post-operative period. It can

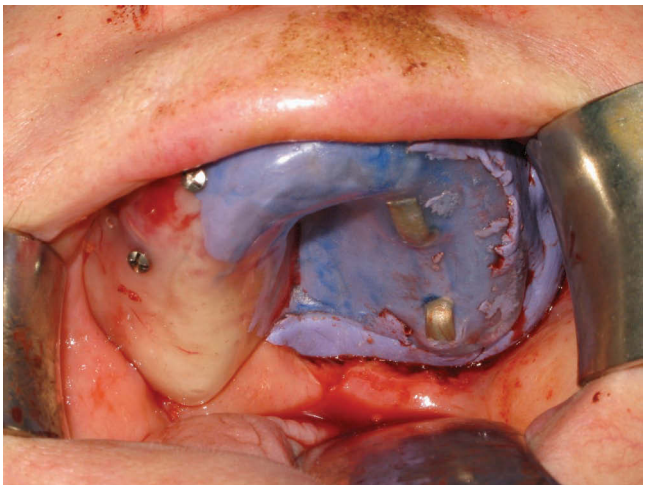


Figure 31.6 A screw retained surgical obturator relined with silicone putty.

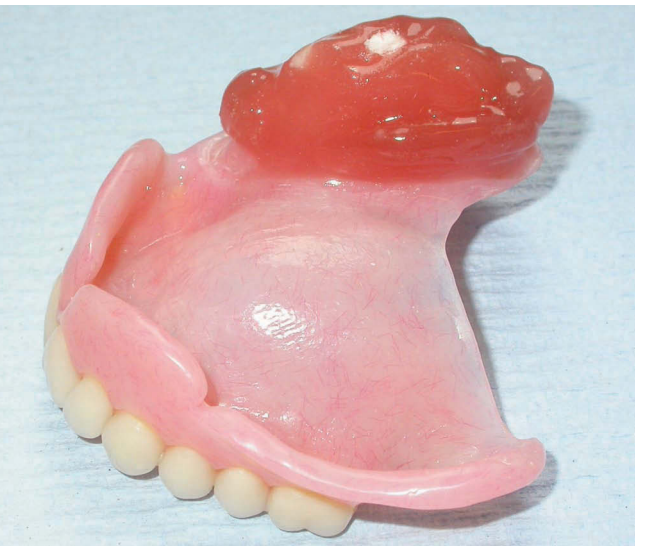


Figure 31.7 A simple maxillary obturator prosthesis with integral soft bung to engage defect undercuts.

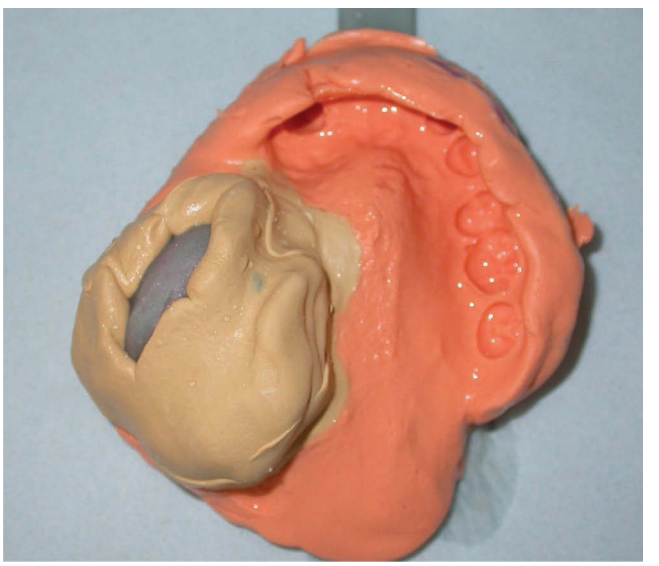


Figure 31.8 A multi-part dental impression.

also assist with haemostasis where there is residual oozing from within the defect.

The fixation of the surgical obturator will depend on the defect size as well as the presence of remaining teeth and residual alveolar bone in the maxilla. Where the defect is small and there are plenty of remaining teeth, dental retention utilizing clasps will usually suffice. In larger defects, additional retention is often required utilizing bone screws and/or circum-zygomatic wires (**Figure 31.6**).

Post-operatively the surgical obturator will require removal and modification as the defect heals and begins to change in dimensions. Smaller defect cases can often be managed in the outpatient clinic whereas larger defects may require a return to the operating room especially where circum-zygomatic wires have been employed as a means of retention. The surgical obturator is generally left *in situ* for 1–3 weeks before it is modified and relined to improve its oro-nasal/oro-antral seal and general comfort for the patient. The patient is instructed on how to remove, clean and replace the prosthesis. The patient is followed up on a regular basis with further modifications being made to the prosthesis until such time as further impressions can be made to construct a more definitive obturator.

Figure 31.7 demonstrates the definitive obturator prosthesis for a patient with a low-level partial maxillectomy. The soft silicone bung material assists in the retention of the prosthesis by engaging the natural undercuts in the defect by means of the surgical technique.

MULTI-PART MAXILLARY OBTURATORS AND THE USE OF OSSEOINTEGRATED IMPLANTS

Many patients experience significant trismus following maxillectomy especially where surgery is combined with radiotherapy.[5] This factor must be taken into account when planning prosthetic obturation of maxillary defects and may lead to the decision to remove further teeth to allow access for the obturator. In partially dentate patients, significant trismus can lead to difficulties in the access for impression making and indeed in the placement and removal of the prosthesis. In many cases, impressions need to be taken in several parts (**Figure 31.8**) and the definitive obturator can also be fabricated with a separate obturator component which is joined intra-orally with the dental prosthesis component. **Figure 31.9** demonstrates this approach for a low-level maxillectomy defect in the posterior maxilla. The obturator component is inserted directly into the defect initially and attaches to the overlying dental prosthesis by means of a magnet embedded into the acrylic surface of the obturator component which combines with another magnet in the intaglio surface of the dental prosthesis.

Where more extensive maxillary defects are to be obturated or in the edentulous patient where retention

Figure 31.9 A 2-part obturator with magnet linkage.

difficulties are anticipated, the use of osseointegrated dental implants may be employed. Mostly these retention aids should be placed at the time of resection especially if radiotherapy is to be utilized post-operatively. **Figure 31.10** demonstrates the use of zygomatic implants to retain a large maxillary obturator in an edentulous patient. These implants achieve very high initial stability and can be used at a very early stage to support the obturator. In this case, the implants are splinted together with a retentive bar to retain the obturator. In such cases, the extent to which the prosthesis needs to engage into the defect is much reduced as this is not required for its retention.

PROSTHETIC MANAGEMENT OF FACIAL DEFECTS

The use of facial prostheses to reconstruct surgical or congenital defects of the nose, mid-face, orbit and external ear is well established and is reviewed very nicely in a recent review article by Ariani et al.[6] The use of silicone-based facial prostheses is a highly effective way of providing the patient with an aesthetic tissue replacement in situations where surgical reconstruction with autologous tissue would be extremely challenging or not possible due to anatomical constraints or patient fitness. The construction of such bespoke prostheses requires great skill on the part of the prosthetic technician and careful planning on the part of the surgical team and maxillofacial prosthodontist to provide a defect of adequate dimensions and with appropriate retentive elements. Whilst the use of skin adhesive products together with the use of mechanical features such as defect undercuts and spectacle frames were the main methods to retain facial prostheses, the last 30 years has seen a shift to retention of facial prostheses with osseointegrated implants.[7-9] Whilst conventional adhesive retained prostheses still have their role, patients find them difficult to locate, subject to dislodgement during daily functions as well as suffering from skin irritation.[10]

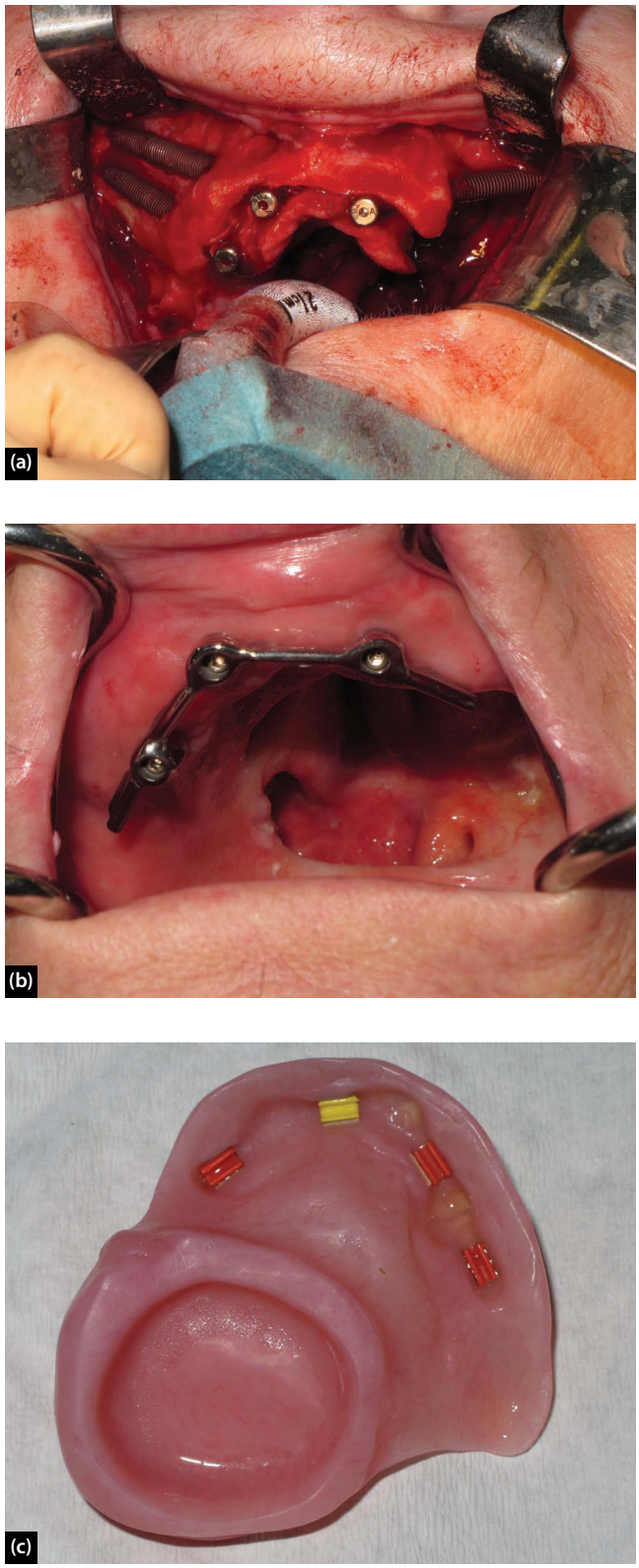


Figure 31.10 The use of zygomatic implants to retain a maxillary obturator prosthesis. **(a)** Multiple zygomatic implants placed at the same time as a left-sided maxillary resection. **(b)** Zygomatic implant retained bar to provide improved support and retention for the removal of the maxillary obturator. **(c)** Maxillary obturator with ink-well obturator componenet and retentive components to fit onto zygomatic implant bar.

A number of pre-prosthetic surgical techniques are widely accepted in order to maximize the benefit from the facial prosthesis[11] depending on the area concerned. Small areas of unsupported tissue should be removed, where possible, to provide a solid margin to support the periphery of the prosthesis. A suitable cavity should be provided to accommodate the prosthesis and this is especially true in mid-face and orbital cases. If possible, the bulk of vascularized flaps in this area should be kept to a minimum or subsequently debulked prior to prosthesis construction. Sharp bony margins of the resection should be smoothed and the use of split-skin grafts is encouraged especially within the orbit as, once healed, they can provide a stable, hair free, and drier surface.

Where rhinectomy is undertaken, preservation of the nasal bones, when oncologically safe, is advantageous as it provides useful vertical support for the prosthesis and for spectacle wear. Reduction of the projection of the nasal septum helps create space within the defect for implant frameworks, where these are employed, and also helps reduce secretions in the area of the prosthesis.

A variety of endosseous implant types have been successfully employed to retain facial prostheses ranging from very short (3–5 mm) 'extra-oral' implants, conventional 'dental' implants and very long (30–55 mm) zygomatic implants.[9]

Figure 31.11 demonstrates the use of horizontally placed zygomatic implants to retain a large mid-face prosthesis.

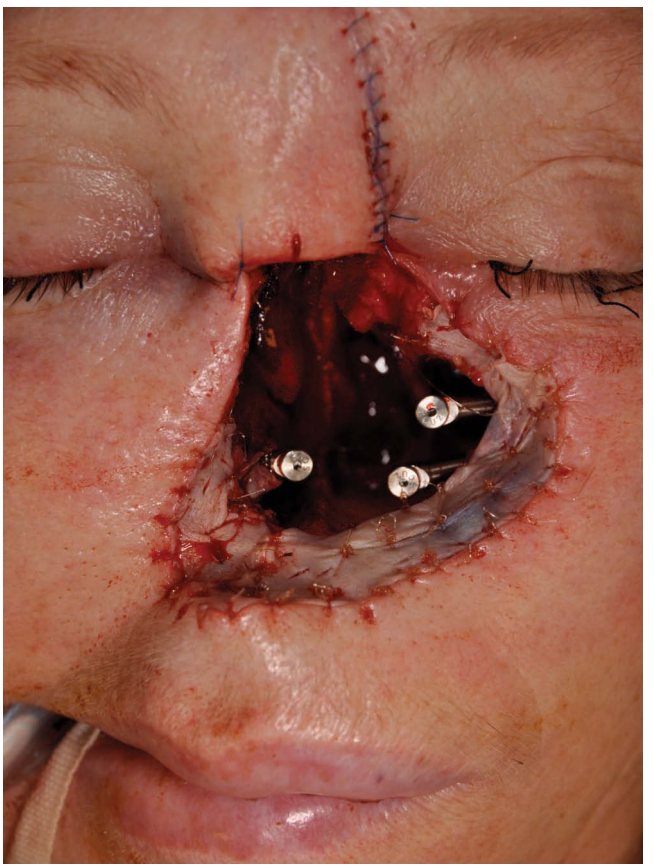


Figure 31.11 Horizontally placed zygomatic implants used to retain a large mid-face prosthesis.

DENTAL ACCESS SURGERY TO ASSIST TRANS-ORAL PROCEDURES

Trans-oral surgery is increasingly used in the management of benign and malignant processes. However, access for such techniques can be hampered significantly by a range of factors such as trismus, a class 2 skeletal profile and the presence of maxillary anterior teeth. Alternative trans-oral techniques have been reported for pharyngeal pouch repair in patients with trismus[12] as open surgery is perceived to hold higher morbidity for patients. The use of dental extractions to facilitate trans-oral ENT procedures is rarely reported but should be considered in conjunction with the maxillofacial prosthodontist as a means of facilitating surgical access.[13] Tooth replacement with fixed or removable dental prostheses can be subsequently provided depending on the patient's presenting dental status and wishes.

RESTORATION OF THE DENTITION FOLLOWING ABLATIVE SURGERY

Patients presenting with head and neck cancer often present with significant dental issues at time of presentation.[14] There are high levels of dental phobia and anxiety reported in this population of patients and this often results in a degree of dental neglect. Many patients are elderly and a significant proportion of patients are edentulous at the time of presentation. In addition, resective surgery for malignant tumours within or adjacent to the maxillary and mandibular alveolar bone require the removal of sections of the dentition either as a rim or segmental resection to achieve oncologically safe margins. The resulting post-surgical condition of oral cancer patients is therefore highly varied and each one presents a range of challenges in respect to successful dental rehabilitation. Soft and hard free-tissue reconstruction techniques can often lead to the presence of residual bulky soft tissue skin flaps overlying the jaws obstructing the dental envelope (**Figure 31.12a**).

However, there is little doubt that the use of composite free flaps to reconstruct segmental jaw defects has very much improved outcomes for patients and can usefully provide a foundation for osseointegrated implant insertion in selected cases.[4]

Decisions regarding the dentition need to be made prior to surgery to ensure that the patient's subsequent oral function is maximized and that untreated dental pathology does not remain untreated. The patient's wishes and motivation regarding their dentition and subsequent rehabilitation should be taken into account along with their habitual risk factors, the site, extent and behaviour of their presenting tumour and their predicted prognosis. Where radiotherapy is to be used as an adjuvant treatment, the dose, fields and fractionation of treatment and their likely effect on the remaining dentition should be carefully considered when arriving at a suitable treatment plan for the dentition.

Where dental rehabilitation is to be provided, the aims, advantages and limitations of treatment should be

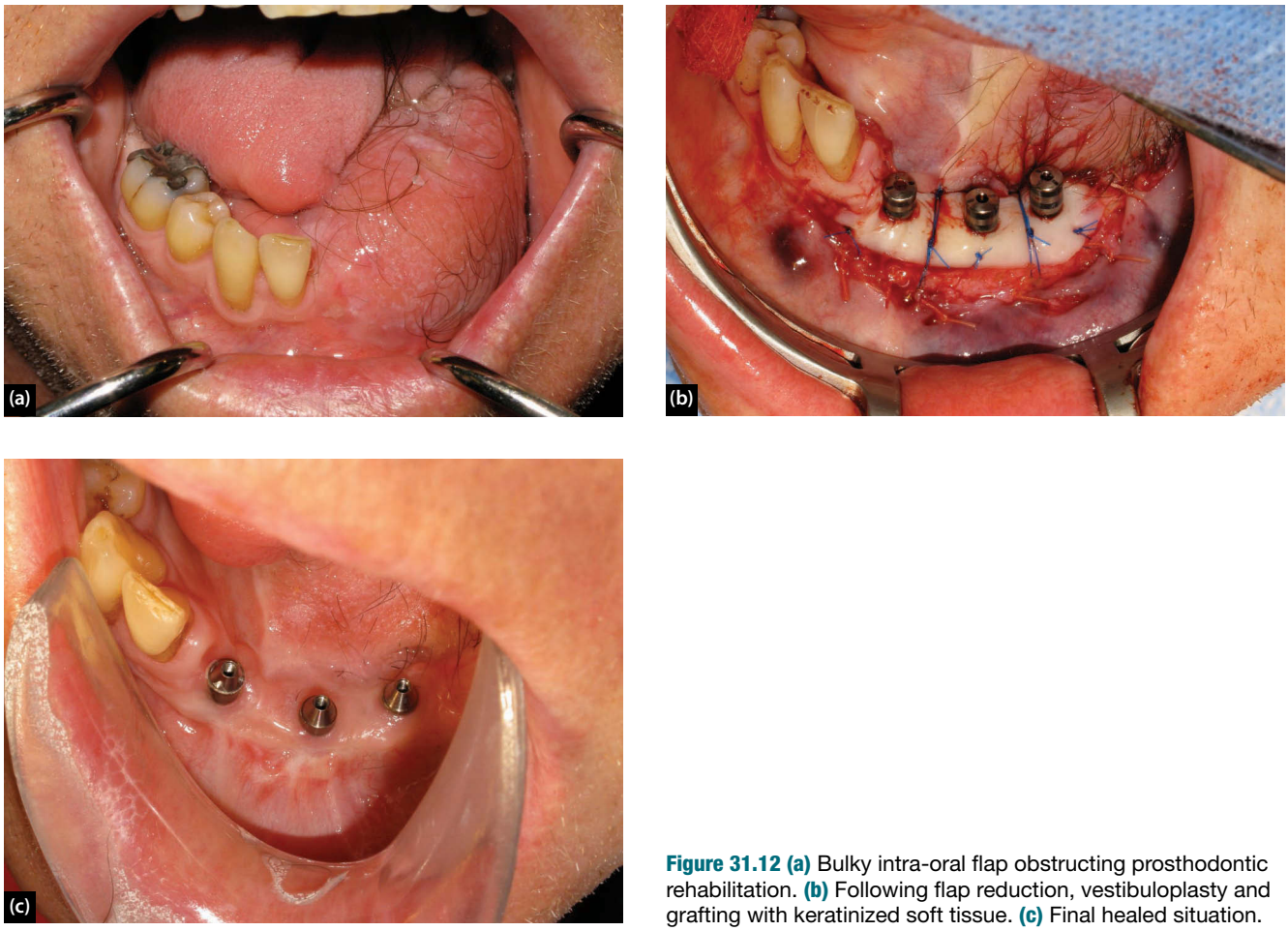


Figure 31.12 (a) Bulky intra-oral flap obstructing prosthodontic rehabilitation. **(b)** Following flap reduction, vestibuloplasty and grafting with keratinized soft tissue. **(c)** Final healed situation.

acknowledged with the patient. Whilst patients can benefit enormously from the cosmetic improvement in appearance following prosthodontic treatment, they are often left with functional problems associated with chewing and swallowing and these are to a large part associated with the degree to which their overall tongue function has been affected by the cancer treatment modalities. In addition, patients always tend to favour chewing on their non-resected side following jaw resection so restoration following a small posterior mandibulectomy is often not required if the patient has a good complement of remaining functional natural teeth.

A small number of patients can receive, tolerate and function reasonably well with conventional fixed and removable dental prostheses following surgery but the majority of patients who have undergone reconstructive procedures within the mouth are often left with aberrations in intra-oral anatomy that are difficult to overcome with simple dental prostheses alone. It is in this context that the maxillofacial prosthodontist relies on the use of osseointegrated implants to overcome these difficulties.

Primary dental implant placement

In some carefully selected patients, there will be a case for the immediate installation of osseointegrated implants at the time of primary resective surgery in order to provide a future effective prosthetic dental rehabilitation within a reasonable timescale (**Figure 31.13**). The placement of implants at the same time as the resective surgery has a number of advantages and potential disadvantages (**Table 31.1**) although a recent systematic review[15] has shown that this is a highly effective treatment in facilitating dental rehabilitation with high levels of implant survival, despite subsequent post-operative radiotherapy.[16] The majority of patients (75%) go on to complete their dental rehabilitation and show improvements in their quality of life (QOL). Not surprisingly, patients receiving post-operative radiotherapy report poorer QOL scores than their counterparts who did not require radiotherapy.[17]

The use of primary osseointegrated implants has been reported mainly in patients with intact mandibles who are undergoing soft-tissue oral resections although there are smaller case reports/case series with placement directly into composite flaps[18] (mainly fibula flaps for mandibular resections) as well as into the maxilla and zygomatic complexes for patients undergoing maxillectomy.[19] Implants should be placed by or in close conjunction with the maxillofacial prosthodontist to ensure that the best prosthodontic result is obtained. The placement of implants into composite free flaps at the time of jaw reconstruction is however fraught with difficulty and there is evidence to suggest that such patients should be treated secondarily.[20]

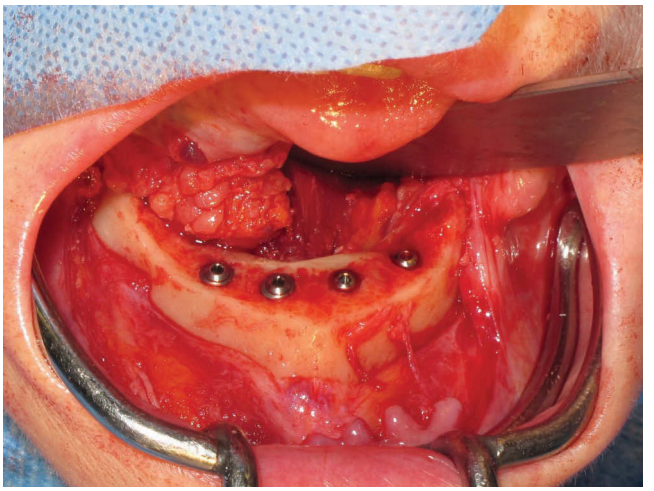


Figure 31.13 Insertion of dental implants into the anterior mandible simultaneously with tumour resection from the floor of mouth.

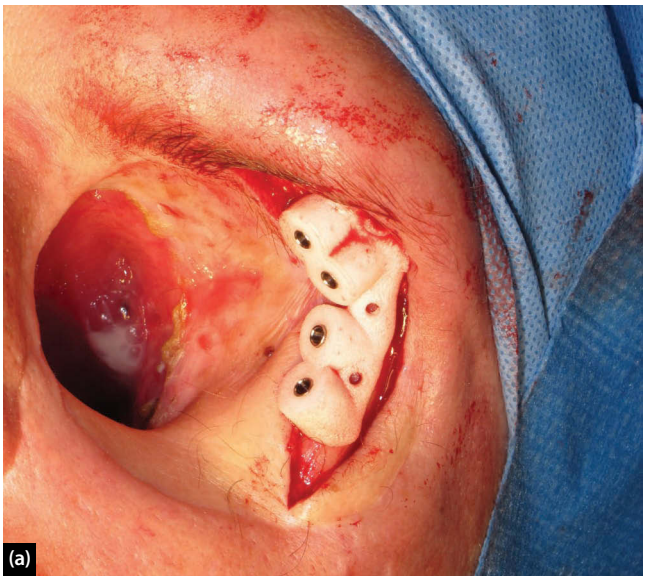
TABLE 31.1 Advantages and disadvantages of primary osseointegrated implant placement

Advantages	Disadvantages
Early rehabilitation	Unknown prognosis for patient
Implants placed before radiotherapy	Unknown oral function post surgery
Psychological patient benefit	Anatomical difficulties for placement
Reduced number of surgeries	Cost implications if implants not used

Rohner et al.[21] described the use of 'pre-fabricated' fibula flaps into which implants are installed by means of CT-based computerized planning and guided surgical techniques with their subsequent transfer to the defect and immediate restoration with a dental prosthesis.. This technique however is not yet in widespread use and is not yet applicable to routine jaw resections required for malignant disease.

Secondary dental implant placement

For many patients, any decisions regarding dental rehabilitation should be left till the patient has fully recovered from the effects of the cancer treatments, their functional deficits identified and their response to the treatment in terms of disease control established. Their motivation for treatment should be ascertained and detailed prosthodontic planning undertaken prior to intervention. CT-based computerized planning techniques are useful where composite reconstructive techniques have been used as they assist in establishing whether adequate bony union has been established following surgery, the presence and position of osteosynthesis plate and screw materials, localized anatomy and the relationship of the proposed prosthesis to suitable implant positions. The use of stereolithographic surgical drilling guides can be helpful in transferring



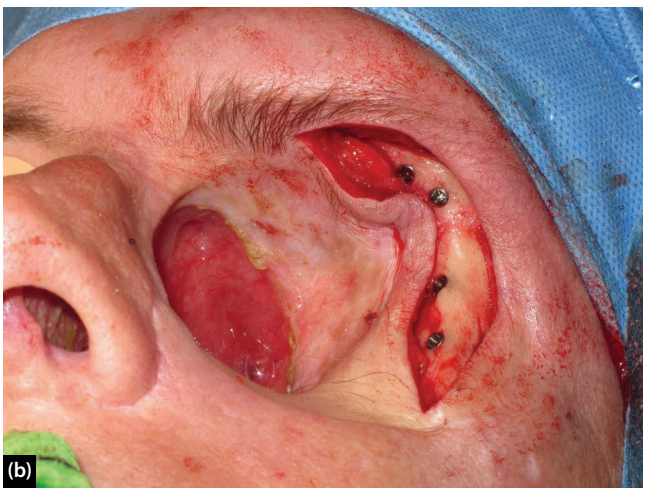


Figure 31.14 (a) The use of a stereolithographic surgical template to guide placement of orbital rim implants. **(b)** Dental implants positioned in the orbital rim according to the pre-operative computer planning.

detailed computer-based planning to the clinical situation (**Figure 31.14**).

Management of the peri-implant soft tissue is another important aspect of care as inevitably excess tissue is present prior to treatment. Reduction and tailoring of skin flap tissue overlying the jaw around the implant fixtures is recommended to allow easy access to the implant, to produce immobile tethered peri-implant tissue and where possible to fashion a new buccal sulcus adjacent to the implants, to facilitate future oral hygiene measures (**Figure 31.12b**). Where radiotherapy has not been used, more aggressive reduction of the soft tissues is possible in conjunction with soft-tissue grafting using palatal mucosa[22] or split-skin grafts[23] to obtain ideal results often with the use of an implant retained dressing plate. In the irradiated patient, simple thinning of the overlying tissues is often all that can be done without risking mucosal breakdown and potential bone exposure.

Implant placement in irradiated jaws

The use of dental implants in the management of irradiated oral cancer patients has been a controversial subject over many years with reports of poor implant survival (as low as 50%) being reported within the literature in some centres.[24, 25] Clearly, radiotherapy is a significant risk factor for failure in these patients and must be carefully considered when planning treatment strategies. However, more recent data are much more encouraging with a recent comprehensive meta-analysis demonstrating an overall mean survival of 83% (range 34–100%) with a mean follow-up of at least 5 years.[26] This study demonstrated no statistically significant differences in survival between implants in irradiated and non-irradiated native jaws but highlighted poorer survival for implants placed into irradiated grafted bone. Changes in implant design, 3-dimensional prosthodontic planning as well as improved / minimalized surgical techniques may account for this improvement in outcomes.

The use of hyperbaric oxygen treatment prior to placement in the irradiated jaw has received much attention with varying results in the literature. Currently there is inadequate information to support its routine use for this indication.[27]

KEY POINTS

- Patients requiring prosthetic rehabilitation for oral and facial defects should be seen pre-operatively with a maxillofacial prosthodontist and anaplastologist.
- Patients requiring a facial prosthesis invariably benefit from osseointegrated implant insertion together with surgical modifications of the resulting defect to maximize the success and aesthetics of the final prosthesis.
- Carefully selected patients should receive osseointegrated implants at the time of resective surgery to maximize dental rehabilitation.
- Osseointegrated implants have high success rates and contribute significantly to improved QOL outcomes in oral, dental and facial prosthetic rehabilitation.
- Radiotherapy reduces implant success and reduces QOL gain from dental prostheses but the use of implants is still of great value in patients who have received radiotherapy.

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CHAPTER 32

MULTIDISCIPLINARY TEAM WORKING

Andrew Davies, Nigel Beasley and David Hamilton

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SEARCH STRATEGY

Data in this chapter may be updated by a Medline search using the keywords: interdisciplinary communication, cancer, decision making, communication, head and neck neoplasms and personal autonomy.

INTRODUCTION

The Oxford English Dictionary defines multidisciplinary as 'combining or involving several academic disciplines or professional specialisations in an approach to a topic or problem'.[1] The UK Department of Health has defined the multidisciplinary team (MDT) as a 'group of people of different health-care disciplines, which meets together at a given time (whether physically in one place, or by video or teleconferencing) to discuss a given patient and who are each able to contribute independently to the diagnostic and treatment decisions about the patient'.[2]

Before the early 1990s only a relatively small proportion of cancer patients benefited from their care being managed by a MDT of cancer specialists. Such teams had existed for decades for some cancers in some hospitals but this was the exception not the rule. In the last 15 years MDT working has been deemed to be the standard of care in the management of all types of cancer. In the UK, the drivers for the development of MDT working were the 'Calman-Hine report',[3] the 'The NHS Cancer Plan',[4] the National Institute for Clinical Excellence's Improving Outcomes Guidance,[5]and the ongoing cancer peer review process.[6]

MULTIDISCIPLINARY TEAM WORKING

Multidisciplinary team (MDT) working is seen as the modern standard of care in cancer treatment decision-making.[5] This means that every cancer treatment decision in the UK should be made under the auspices of an MDT. A survey of 2000 MDT members in September 2009 found that there is an overwhelming consensus that MDTs are beneficial to patient care and should remain the cornerstone of cancer treatment.[7] MDTs bring together staff with the necessary knowledge, skills and experience to ensure high quality diagnosis, treatment and care for patients with cancer. MDT working has been advocated in each of the NICE Improving Outcomes Guidance reports and is strongly supported by clinicians.[8]

Despite this enthusiasm from clinicians, the evidence base for MDT working is weak, with most studies looking at outcomes before and after the introduction of the MDT. These studies are confounded by increasing sub specialization, centralization of care and improvements in diagnosis and treatment. However there is increasing evidence that MDTs do improve some clinical outcomes, patient experience and the working lives of team members. The challenges faced when assessing the impact of MDT working on survival in cancer was outlined by Hong et al. in their systematic review on this subject.[9] The definition of MDT is applied variably across centres and any benefits demonstrated may reflect a selection bias of patients with a better prognosis, rather than a real effect.[9] Hong's review included 21 studies which were categorized broadly into retrospective studies and those with cohorts before and after the introduction of an MDT, usually

in a single centre: it was not able to demonstrate a link between MDT working and survival.

There are no randomized controlled trials of MDT working, as it is now ubiquitous. However, in Glasgow, MDT working was introduced into one health board (the 'intervention area'), before other health boards in the west of Scotland (the 'non-intervention area'), allowing a comparison between two similar populations.[10] Before MDT working was introduced, breast cancer mortality was 11% higher in the intervention area than in the non-intervention area. After MDT introduction, breast cancer mortality was 18% lower than the non-intervention area. There was also a reduced variation in survival between hospitals in the intervention area. This study used cancer registry data on 13 722 patients, and the authors adjusted for temporal trends. This large study was published after the systematic review above and the authors provided detail about the definition of MDT working used. Although only one single study in one cancer, the size of the effect is noticeable and it provides the strongest evidence of a positive effect of MDT working on cancer survival to date.[10] Despite this, given the overall weight of evidence, it is not known if MDT working has an effect on cancer survival. Importantly, however, there is equally no convincing evidence of a negative effect. However, even if MDT working did improve survival, the aspect of the process which was responsible for such effects is not known.

MDT working is popular amongst the members of staff who attend it.[7] Specifically in head and neck cancer, a qualitative study of 33 professionals in four focus groups found that the team provided an inclusive environment for planning care. Staff members reported that the team gave support, a chance to stay up to date and an opportunity for discussing difficult cases.[11] However, MDTs are also expensive: best practice guidelines estimate that a radiologist will take 2 hours and a pathologist 2.4 hours to prepare for each hour of team meetings[12] putting the estimated cost of all UK MDT meetings at £50 million a year for preparation and the same amount again for attendance.[13]

MDTs that work well are characterized by clear aims and a shared understanding of goals, clear systems and processes for managing communication and conflicts, and responsive and proactive leaders who run effective team meetings, provide access to resources and reward excellence. These teams can improve patient outcomes and cost effectiveness in a range of settings from primary care to complex hospital care including stoke, cardiac and musculoskeletal conditions. However, MDTs must be supported to work effectively together. The Interdisciplinary Professional Education Collaborative have suggested the following interventions to support MDTs:[14]

- encourage teams to invest time in developing a shared aim
- develop team skills through practice and reflection
- pay attention to internal team relationships
- identify changes in the educational infrastructure required to help sustain interprofessional learning
- use multiple methods of communication to bridge barriers of schedules and geography.

While it is recognized that the evidence base for the value of for MDT team working in clinical decision making is diverse and of limited quality, studies have concluded that time pressures, a lack of information, a lack of nursing input and poor team leadership can have a negative impact on team decision making. Lamb et al. suggest that the 'inclusion of multidisciplinary cancer teams, preparation time into team-members job plans, making leadership skills training available and obtaining more extensive input from nursing personnel should be considered at the national policy level'.[15]

Effective MDT working should result in the outcomes outlined in **Box 32.1**. These outcomes are expected to be more likely in MDTs with a focus on[16]

- teams with the right membership, good attendance, strong effective leadership and opportunities for personal development and training
- good preparation for well organized meetings in the right physical environment with appropriate technology to support effective communication
- patient-centred clinical decision-making
- good team governance and support, with regular data collection and discussion of patient outcomes.

MULTIDISCIPLINARY TEAM WORKING IN HEAD AND NECK ONCOLOGY

In the UK, the National Institute for Clinical Excellence's Improving Outcomes Guidance for Head and Neck Cancer[5] endorses MDT working, together with centralization of

BOX 32.1 Putative benefits of multidisciplinary team working[16, 17]

- treatment and care being considered by professionals with specialist knowledge and skills in the relevant aspects of that cancer type
- patients being offered the opportunity to be entered into high quality and relevant clinical trials
- patients being assessed and offered the level of information and support they need to cope with their condition
- continuity of care, even when different aspects of care are delivered by different individuals or providers
- good communication between primary, secondary and tertiary care
- good data collection, both for the benefit of the individual patient and for the purposes of audit and research
- improved equality of outcomes as a result of better understanding and awareness of patients' characteristics and through reflective practice
- adherence to national and local clinical guidelines
- promotion of good working relationships between staff, thereby enhancing their job satisfaction and quality of life
- opportunities for education/professional development of team members (implicitly through the inclusion of junior team members and explicitly when meetings are used to devise and agree new protocols and ways of working)
- optimization of resources – effective MDT working should result in more efficient use of time which should contribute to more efficient use of NHS resources more generally.

cancer services at regional cancer centres (serving a population of over one million people). Moreover, the guidance states that patients should be managed by MDTs treating at least 100 related cases per annum. Studies suggest that such centralization of services is associated with improved outcomes in head and neck cancer.[18] The guidance recommends that specialized MDTs manage patients with thyroid cancer, patients with salivary gland tumours and patients with skull-base tumours. In addition, the guidance recommends that patients with a sarcoma of the head and neck region should be managed in conjunction with the regional sarcoma MDT.

Box 32.2 shows the suggested core membership for a head and neck cancer MDT in the UK;[5] the guidance characterizes the role of each member of the core team for example clinical nurse specialist, speech and language therapist, dietician. The diverse membership of the core team is essential as almost all patients with head and neck cancer require assessment and management of the airways, speech, nutrition, appearance and pain. **Box 32.3** shows the suggested extended membership for a head and neck cancer MDT in the UK.[5] The members of the extended MDT are there to manage certain patients and, as such, are not required to attend all MDT meetings (in contrast to the members of the core MDT). Specialized MDTs managing thyroid, salivary and skull-base tumours have a different membership to head and neck cancer MDTs. For example, the thyroid cancer MDT should include endocrinologists and nuclear medicine specialists.[5] A national audit published in 2003 highlighted that a high level of attendance was not always being achieved in head and neck cancer: although over 95% of meetings were attended by an oncologist and/or a surgeon and 80% were attended by a speech and language therapist, fewer MDTs had access to other specialists. Only around half included dietitians and/or clinical nurse specialists, and the role of other specialists was even more variable, with teams having a mix of plastic surgeons, restorative dentists and palliative care physicians.[19]

BOX 32.2 Recommended core members of the head and neck cancer multidisciplinary team[5]

Core members

- Surgeons (≥ 3) – the surgeons are likely to be ear, nose and throat (ENT), maxillofacial, or plastic surgeons
- Clinical oncologists (x 2)
  - Restorative dentist
  - Pathologists
  - Radiologist
  - Clinical nurse specialists
  - Speech and language therapist
  - Senior nursing staff from the head and neck ward
  - Palliative care specialist
  - Dietitian
- Team secretary
  - Data manager
  - MDT co-ordinator – the co-ordinator may also take the role of team secretary and/or data manager

EVIDENCE-BASE FOR MULTIDISCIPLINARY TEAM WORKING IN HEAD AND NECK CANCER

The evidence-base for MDT working in head and neck cancer is as diverse as that for other MDTs, with the same enthusiasm from clinicians, but similar problems with study design and confounding variables such as increasing subspecialization. The primary problem with assessing the effectiveness of the MDT is deciding what the measure should be and from which viewpoint it should be measured. A survey of head and neck cancer MDT members from the UK reported that 90% thought MDT discussion resulted in improved timeliness of tests and treatment, 74% thought MDT discussion resulted in improved patient choice, 71% thought that MDT discussion resulted in improved patient involvement in decisions, 95% thought that MDT discussion results in an increase in proportion of patients staged, and 90% thought that MDT discussion results in improved survival rates.[20]

Wheless et al. reported on a prospective study of the effect of MDT meetings on the management of patients with benign and malignant head and neck tumours.[21] Patients were initially assessed by the 'referring attending physician', and the diagnosis, stage of disease and treatment plan recorded. Subsequently, patients were reviewed at the multidisciplinary 'tumour board', and the diagnosis, stage of disease and treatment plan again recorded. The MDT meeting resulted in a change on diagnosis in 1% patients with cancer (6% patients with benign tumours), a change in stage in 12% patients with cancer, and a change in treatment in 24% patients with cancer (6% patients with benign tumours); in the patients with cancer, the treatment was escalated in 15% cases, de-escalated in 5%

BOX 32.3 Recommended extended members of the head and neck cancer multidisciplinary team[5]

Extended members

- Other specialist surgeons
- Anaesthetist
- Gastroenterologists, radiologists, surgeons and other health professionals with expertise in gastrostomy creation, feeding tube placement and support for patients who require tube feeding
- Ophthalmologist
- Pain management specialist
- Nuclear medicine specialist
- Therapeutic radiographer
- Maxillofacial/dental technician
- Dental hygienist
- Social worker
- Benefits advisor
- Liaison psychiatrist
- Clinical psychologist
- Counsellor
- Physiotherapist
- Occupational therapist

cases and changed to a different modality in 4% instances. In a similar study, Brunner et al. found that in almost a third of cases the treatment plan of the referring clinician was changed by the MDT.[22] Treatment plans were more frequently altered if the original plan from the referring clinician did not include surgery or if the histology was not squamous cell carcinoma or skin malignancy. Kee et al. attempted to ascertain if, when a clinician presents their patient at the MDT, the ensuing discussion changes the reported preference of the clinician.[22] In a similar proportion of cases (39%) the preference of the referring clinician did not match the final decision of the MDT. Interestingly however, they also showed that in only 26% of cases where the team and individual clinician disagreed did the referring clinician finally concur with the decision of the team and present it to the patient.[23]

Kelly et al. reported on a retrospective study of the effect of MDT working on so-called 'clinical quality indicators' associated with the management of patients with head and neck cancer.[24] The introduction of the MDT was associated with an increase in PET scanning as a staging investigation, an increase in pre-treatment dental assessments, an increase in pre-treatment nutritional assessments, an increase in the use of chemoradiotherapy for locally advanced cancer, and a decrease in the time period between surgery and post-operative radiotherapy. Birchall et al. reported on a re-audit of the effect on implementing 'consensus standards' (including multidisciplinary head and neck clinics) on the 2-year survival of patients with head and neck cancer.[25] The study compared patients managed in a number of hospitals during two time periods (1996–1997 and 1999–2000). The authors reported that the proportion of patients seen in an MDT increased from 46% to 74% between the two audits and the number having pre-treatment imaging and accurate staging work-up also increased. The overall survival between the two cohorts was not significantly different (64.1% increased to 65.1%), but analysis revealed that those patients were assessed in an MDT had a statistically significantly better survival than those who were not.[25] Although MDT working could have improved the 'non-temporal' standards such as pre-treatment imaging, the correlation between MDT working and increased survival cannot be assumed to be causative. The authors discussed that survival data was probably incomplete, as the deaths reported did not match those of death registrations in the area. Also, temporal trends were not accounted for and confounding factors such as patient selection were not acknowledged.[25]

Similarly, Friedland et al. reported on a retrospective study of the effect of MDT working on the 5-year survival of patients with head and neck cancer.[26] The study compared patients managed by the MDT vs patients managed outside of the MDT within the same hospital over a 12-year period. There was no difference in survival in patients with stage I–III disease, but there was statistically (and clinically) significant improvement in survival in patients with stage IV disease who were managed by the MDT. The authors suggested that the improvement in survival was primarily related to an increase in the use of multimodal therapy, and specifically the use of concomitant chemotherapy and radiotherapy. However, the allocation to management within or outwith the MDT was not randomized, but chosen by the referring clinician; also the MDT patient group had a higher age and more advanced disease. Most importantly however, it is not made clear why some patients were selected to be managed by the MDT whilst others were managed by individual clinicians.

OTHER ISSUES

Patient autonomy

The MDT lacks one important voice, that of the patient.[27] There are little data documenting the patient experience of involvement in MDTs, as it is rarely routine practice: small studies have concluded that patients attending their own MDT allows for better information giving but not necessarily improved involvement in decision-making. Many teams adopt a 'democratic forum model', whereby patients are informed of the decision of the MDT and can accept or decline the treatment proposed. This lacks patient involvement. Shared decision-making (SDM) is a process in which both clinicians and patients work together choosing treatments based on the best available clinical evidence and the patient's preferences. Patients are given information about options, outcomes and uncertainties, and after discussion agree a treatment plan.[28] This concept has been used by Sharma et al. in creating the 'MDT approval model' (**Figure 32.1**).[29] This involves patients in the decision-making process at the very first visit with the patients views taken to the MDT for discussion by the clinical team. Nevertheless, the area of Inter-Professional Shared Decision Making (IP-SDM) is in its infancy as the majority of the research on SDM concentrates on the physician/patient dyad.[30, 31] In two recent systematic reviews of measures to help the implementation of SDM, only 3/40 studies focused on the interdisciplinary approach.[32, 33] Stacey et al. performed a large literature review and theory analysis which identified no models of SDM in the interprofessional context.[34]

Omitting, or not incorporating, patient preference information into the treatment discussion potentially has an effect on decision implementation. In three studies of the implementation of the MDT recommendation in the clinic 'patient choice' caused a change in, or rejection of the MDT recommendation in between 2% and 5% of cases.[35–37] At the same time, patient-centred care is important to MDT members. In the NCAT Survey of MDTs, 95% of respondents felt that 'patient views should always inform the decision-making process' and 'patient views/preferences should be presented to the MDT by somebody who has met the patient'.[7] When the free-text responses from the NCAT survey were analyzed, lack of information about the patient or lack of knowledge of the patient views were seen as the main reason for MDT decisions not being implemented.[38]

Various quantitative measures have attempted to measure the 'patient centredness' of the MDT discussion.

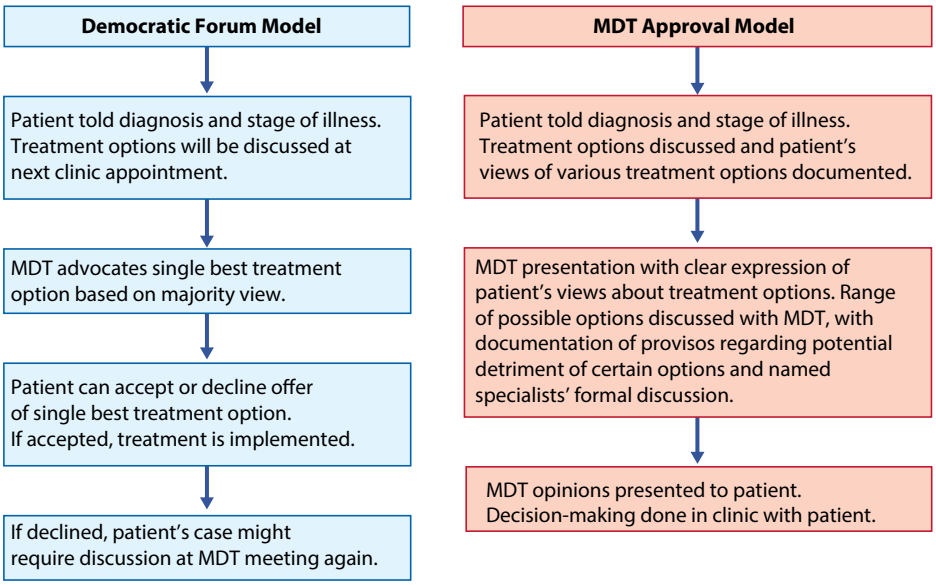

Figure 32.1 Democratic forum model and MDT approval model of decision-making.[29]

Taylor et al. measured the patient-centredness of the MDT decision by counting the number of cases where there was a mention in the MDT discussion of patient-based information.[39] Patient-based information in this study was defined as patient demographics, comorbidities, supportive needs or patient and family preferences. Eight out of the ten observed meetings scored 'poor' or 'very poor' for patient-centred care. The patient information which was included was frequently confined to demographics and most teams rarely considered other patient-based factors. Lamb et al. developed a tool which used Likert scales to quantify 11 aspects of MDT team discussion, including information about the patient, contribution of members of the team and the incorporation of patient views.[15] Teams scored highly in the amount of information given about the clinical history, and radiological information. Teams were found, using this scale, to incorporate patient views into the discussion quite poorly. Moreover, the self-assessment questionnaires completed by the team members suggested that they overestimated the 'patient-centredness' of their decisions.

Qualitative studies have gone further in analyzing how MDT discussions include the patient. Kidger et al. conducted observations and interviews of MDT members and found that the consideration of patient-related factors such as comorbidity information, psychosocial issues and patients' wishes was unstructured when compared with the very structured manner in which the biomedical information was presented.[40] MDT members recognized the importance of 'seeing' a patient rather than an objective representation through information; however information about patient preferences was only really presented when these were strongly held, or ran counter to the recommendation of the team. The team exhibited uncertainty about when and how this kind of information should be incorporated into the discussion. In a similar study, Lanceley et al. reported that the biomedical details of the patient were at the forefront of the discussion, packaging patients into a semi-predictable 'case' which consisted mainly of their biomedical data.[41] Although information such as the ethics of treatment selection or the individuality of the patient was sometimes presented, the team struggled to incorporate this into the 'case' and therefore into the decision. The authors observed that this often led to two strands of narrative about a single patient, which the team had significant difficulties combining.

Clinical decision support systems

Clinical decision support systems are defined as 'systems that are designed to be a direct aid to clinical decision making in which the characteristics of an individual patient are matched to a computerized clinical knowledge base, and patient-specific assessments or recommendations are then presented to the clinician(s) and / or patient for a decision'.[42] Clinical decision support systems have been reported to useful in the MDT, but further research is needed before such technology is introduced into routine clinical practice.[43, 44] Additionally, 'decision aids' are designed to be used before, during or after a clinical consultation by the patient with or without a clinician. In a systematic review of 115 randomized controlled trials, the use of a decision aid was associated with improved patient knowledge, lower decisional conflict, a decreased proportion of patients who were passive in decision-making and fewer patients remaining undecided. There was also a reported increase in patient satisfaction with the decision-making encounter and improved perception of risk.[45] However, most of these studies analyze the use of the decision aid in the context of the clinician-patient dyad rather than an MDT.

MDT working does however allow a new role to be incorporated into the team: that of a decision coach. A decision coach's role is to assess the decisional needs of the patient and then support the patient through decision making, using decision aids and adjuncts if available.[45] Decision coaching can be provided by a member of the team who

is 'trained in decision support and [is] supportive but relatively neutral in the decision'.[46] Decision coaches can help to improve confidence in decision-making and prepare for the decision consultation with positive effects on knowledge, information recall and participation in decision-making.[47, 48] However, in a recently published systematic review, only 10 randomized controlled studies were identified and thus conclusions about the effectiveness of decision coaches were limited. The authors found that although decision coaching can improve patient knowledge, it is difficult to unpick how much of this improvement is due to decision coaching, and how much to the decision aid which is often simultaneously used. The effect on other outcomes such as cost effectiveness, values-choice concurrence and patient satisfaction varies, with some studies reporting a positive effect, and others reporting no difference.[49]

Medico-legal issues

The discussion of a patient at a MDT meeting amounts to a referral to the members of the MDT, and so extends a 'duty of care' to the clinicians within the multidisciplinary care team.[50] As a result, the clinicians are accountable for decisions related to their area of expertise, irrespective of whether or not they contributed to the treatment discussion, and irrespective of whether or not they subsequently treat, or even meet, the patient. It is, therefore, imperative that team members voice any concerns about treatment decisions during the MDT meeting, and ensure that these concerns, and recommendations about alternative treatments, are formally recorded in the documentation relating to the MDT meeting. In such cases, the MDT should inform the patient about the alternative treatment option as well as the 'consensus' treatment option.

CONCLUSION

The creation of formal MDTs ensures that patients are cared for by clinicians with a range of skills, facilitates communication between team members allowing continuity of care, and creates an opportunity for the team to learn together and review patient outcomes against other teams using nationally published datasets.[13]

MDT working is the standard of care in cancer decision-making, however if it is to remain so, the limitations of decision-making in this setting should be acknowledged and overcome. MDT working presents barriers to the incorporation of patient-centred information (such as values, preferences and treatment priorities). If these factors are not taken into account, this may lead to decisions not being implemented, or to a predominance of a paternalistic decision-making style.

Despite the weak evidence base, MDTs are enthusiastically supported by their members and there is increasing evidence that they play an important role in improving patient outcomes and patient experience along with the working lives of team members. Tools are available for teams to reflect on their performance and drive improvement, with a particular focus on regular review of patient outcomes and team relationships.

While there is a recognition that patients with head and neck cancer should be cared for by specialized teams treating large numbers of patients, it is important to emphasize the need to provide care for patients closer to home where possible. Multidisciplinary networks of care providing access to assessment, diagnostics, follow-up and end-of-life care close to home will be vital before further centralization of complex services is considered.

The simple act of bringing together expert clinicians from a wide range of professions and disciplines to discuss and review individual patients and share successes and failures has brought about a revolution in patient management. The head and neck is a diverse and complex cancer site where continuity of care when considering issues with the airway, speech, nutrition, appearance and pain have all been supported by MDT working. Review of outcomes and recruitment into trials will be critical to improving patient outcomes and experience in the future and will all be supported by effective MDT working.

KEY POINTS

- The majority of head and neck cancer decisions in the UK and worldwide are made through a multidisciplinary team (MDT).
- MDT working encourages the involvement of allied health professionals in the assessment, management and rehabilitation of head and neck cancer patients.
- MDT working improves a range of clinical outcomes (such as appropriate staging and clinical trial entry), however, its effect on survival is harder to measure.
- Effective patient involvement in MDT decisions is a challenge and clinicians should develop ways of working which encourage shared decision making.

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CHAPTER 33

NUTRITIONAL CONSIDERATIONS

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SEARCH STRATEGY

Data in this chapter is supported by a Medline search using the following keywords: nutrition, screening, assessment, malnutrition, weight, nutritional intervention, immunonutrition, enteral tube feeding, gastrostomy, PEG, RIG, nasogastric tube (NGT), swallow, dysphagia, xerostomia, quality of life, rehabilitation, survivorship and feeding.

INTRODUCTION

This chapter will look at the nutritional considerations from diagnosis, throughout treatment to rehabilitation and survivorship in patients with head and neck cancer. The chapter aims to provide information on several areas of nutrition including nutritional screening, nutritional interventions during surgical and non-surgical oncology treatments, nutritional support, rehabilitation and survivorship.

THE ROLE OF NUTRITION IN HEAD AND NECK CANCER

It is common for patients with head and neck cancer to report difficulties with eating and drinking at presentation due to tumour location. In addition, dietary habits and lifestyle factors may have further compromised their nutritional intake prior to diagnosis.[1] Studies have estimated that between 44% and 57% of patients experience difficulties in eating or unintentional weight loss prior to commencing treatment.[2, 3] Treatment for head and neck cancer can have negative effects on eating and swallowing which can lead to deterioration of nutritional status.[4] These effects will be intensified with multi-modality treatments. In the surgical patient, weight loss can lead to increased complication rates, such as impaired wound healing, reduced immune function and decreased tolerance to treatment.[5] For patients undergoing radiotherapy, weight loss is associated with increased treatment toxicities, more treatment interruptions, poorer quality of life (QOL) and reduced overall survival.[6–8]

It is widely accepted that weight and Body Mass Index (BMI) alone are inadequate measures of nutritional status. The loss of muscle mass that occurs during cancer-related malnutrition is understood to be the major contributor to reduced functional status, increased mortality and other negative outcomes associated with malnutrition.[9] Nutritional intervention for patients with head and neck cancer aims to identify, prevent and treat malnutrition from the point of diagnosis through the entire cancer pathway. Regular dietetic counselling and weighing may help to motivate patients and improve nutrition outcomes and QOL.[10, 11] A specialist head and neck dietitian should be a key member of the multidisciplinary team (MDT) treating patients with head and neck cancer.[1]

Defining malnutrition

Malnutrition is a state of nutrition in which a deficiency or excess (or imbalance) of energy, protein and other nutrients causes measurable adverse effects on tissue/body form (body shape, size and composition) and function and clinical outcome.[12]

Malnutrition may be defined as:

- a BMI < 18.5 kg/m^2
  OR
- a combined unintentional weight loss of > 10% over 6 months (or > 5% in 3 months), in combination with a reduced BMI or low fat free mass index (age and sex specific).[13]

The definition of malnutrition in cancer patients is complicated by emerging terminology such as cachexia and sarcopenia of which there are no universally accepted definitions. These terms attempt to recognize the loss of lean body mass which is compounded by the systemic inflammation and metabolic disturbances which may arise in patients with cancer.[14] Although not routinely used in clinical practice at this time, such terms are appearing more in the oncology literature as the complex mechanisms involved in cancer-related malnutrition become better understood.

Nutritional status has been recognized as a long-term prognostic factor in patients with head and neck cancers for almost 30 years.[15] Malnutrition in patients with head and neck cancer can have a significant adverse impact on clinical, cost and patient-centred outcomes.

Malnutrition has been associated with:

- delayed wound healing and increased risk of post-operative complications and infections[16]
- impaired cardiac and respiratory function due to muscle weakness
- treatment interruptions[16, 17]
- decreased response rates to chemotherapy
- increased risk of loco-regional failure[18]
- increased length of hospital stay
- depression and poor QOL[19]
- increased mortality rate. [8, 20]

Nutritional screening

Nutritional screening aims to identify patients who are malnourished or who are at risk of becoming malnourished during treatment as early as possible. Patients with head and neck cancer should be nutritionally screened using a validated nutritional screening tool.[10, 21] Whilst there is limited good-quality evidence for screening tools specifically for patients with head and neck cancer, there are several validated for use with cancer patients.[10] These include Subjective Global Assessment (SGA) Tool, Patient Generated SGA (PG-SGA) Tool and Malnutrition Screening Tool (MST).

The SGA assesses nutritional status based on features of a patient's nutritional history and physical examination. The PG-SGA is an adaptation of the SGA for assessing nutritional status and is patient generated. Scores identify patients who are well nourished and those who have developed or are at risk of developing malnutrition during treatment and follow-up.[22] The MST consists of two questions relating to weight history and appetite; it is quick and simple to use and compares favourably with PG-SGA. The Malnutrition Universal Screen Tool (MUST) is used widely in healthcare settings across the UK, however it is not validated in cancer.[12] Early identification of high-risk patients and referral to a specialist head and neck dietitian for assessment should be included as part of the planning for every patient with head and neck cancer when treatment options are being considered.[23, 24] Screening should be repeated at regular intervals during the patient pathway.

TABLE 32.1 Factors to consider for nutritional assessment

Diagnosis, specifically regarding tumour site and staging
Nutritional implications of previous treatments
Aim of current treatment plan: cure vs palliation
Single or multimodality treatment plan
Performance status and comorbidity factors
Physical activity level and functional impairment
Medical history that can affect nutritional intake, e.g. diabetes
Current ability to chew and swallow and the likelihood of further impairment due to treatment
Weight history and % weight loss. If not available, signs of weight loss e.g. ill-fitting clothes/dentures
Measurement of muscle mass and recent changes (e.g. hand grip strength)
Changes to appetite, reduced food intake
Modified eating habits or techniques to make it easier to swallow
Avoidance of foods or drinks that are difficult to chew or swallow
Avoidance of eating meals with others or eating in public
Access to food, food preparation facilities and cooking skills
Lifestyle factors, alcohol, smoking, recreational drug intake
% of energy intake from alcohol
Fluid intake
Employment and financial status
Social support network / support at home

Nutritional assessment

Following screening, a full nutritional assessment should be undertaken for patients identified as nutritionally 'at risk'. This should include consideration of a range of factors, illustrated in **Table 32.1**. Assessment should be completed within a pre-treatment clinic and should be repeated at regular intervals during treatment. It is imperative that patients with head and neck cancer are assessed by a specialist head and neck dietitian, and advised and monitored up to the point of surgery and/or non-surgical treatment with respect to their nutritional status. This enables the best possible outcome from treatment interventions in this

high-risk group and should form an integral part of clinical practice for head and neck MDTs.[4]

Pre-treatment optimization

It is essential to optimize patients with head and neck cancer who are malnourished at presentation. Even patients who are managing reasonably normal intake may struggle to reach their energy and protein requirements without individualized dietetic intervention and/or supplementation in some format. Vital factors to be considered when determining appropriate nutritional intervention for patients are:

- Is there evidence of pre-existing malnutrition, indicating the need for pre-treatment nutritional intervention?

Evidence suggests that correcting nutritional deficiencies before surgery reduces the incidence of post-operative complications.[16] Pre-operative feeding for 7–14 days should be offered to patients who present with severe malnutrition and are planned for major surgery, even if the surgery must be delayed.[25, 26]

- Does the patient have a safe swallow?

If the patient is displaying signs of aspiration they should be referred for assessment by a specialist speech and language therapist (SLT).[27] Dysphagia at baseline is a risk factor for requiring earlier and prolonged enteral tube feeding during treatment and should be considered in the pre-treatment stage.

Nutritional requirements

Cancer itself does not have a consistent effect upon either resting energy expenditure (REE) or total energy expenditure (TEE).[9, 28] Indirect calorimetry to determine REE has a high degree of accuracy however it is not usually feasible in clinical practice. Guidelines suggest the use of standard formulas for healthy subjects for estimating REE with the addition of standard values for physical activity level (PAL).[14] Alternatively, standard equations for energy requirements based on healthy subjects (25–30 kcal/kg/day), may be used.

It is suggested that a protein intake of at least 1–1.5 g/kg/day can help to maintain or restore lean body mass. Intakes up to or above 2 g/kg/day are considered safe in patients with normal renal function.[9, 14]

Requirements for fluid and micronutrients are calculated based on daily recommendations for healthy populations.

Nutritional requirements are summarized in **Table 32.2**. Estimations may be less accurate for severely malnourished, morbidly obese and surgical patients.

TABLE 32.2 Estimated nutritional requirements[9, 14]

Energy	25–30 kcals/kg/day depending on activity level, can increase further if major complications
Protein	1–1.5 g/kg/day
Fluid	30–35 mls/kg/day, this increases in presence of infection or excessive fluid losses
Vitamins and Minerals	As per recommended daily allowance for healthy populations unless considered deficient

TABLE 32.3 Criteria for determining people at high risk of developing refeeding problems[21]

Patient has one or more of the following:

- BMI < 16 kg/m^2
- unintentional weight loss > 15% within the last 3–6 months
- little or no nutritional intake > 10 days
- low levels of potassium, phosphate or magnesium prior to feeding

Or patient has two or more of the following:

- BMI < 18.5 kg/m^2
- unintentional weight loss > 10% within the last 3–6 months
- little or no nutritional intake > 5 days
- a history of alcohol abuse or drugs including insulin, chemotherapy, antacids or diuretics.

Refeeding syndrome

Refeeding syndrome may occur when nutrition support is reintroduced in severely malnourished or starved patients. The syndrome is characterized by metabolic disturbances including hypophosphataemia, hypokalaemia, hypomagnesaemia, altered glucose and lipid metabolism, thiamine deficiency and abnormal fluid balance.[29] These effects may result in life-threatening disturbances of organ function and metabolic regulation.

There are no data on the incidence of refeeding syndrome in patients with head and neck cancer although it is a recognized risk in this population due to the high incidence of malnutrition, history of excessive alcohol intake and requirement for artificial nutrition support. The identification of refeeding syndrome may be problematic in this patient group as their underlying clinical condition and oncological treatment may also result in deranged serum electrolyte levels.

The National Institute of Clinical Excellence (NICE) guidelines on nutrition support, 2006, define criteria for patients at risk of refeeding syndrome (**Table 32.3**).

Although the NICE guidelines provide a useful framework for identifying patients at risk of refeeding syndrome, it is acknowledged that their sensitivity and specificity is low and should be interpreted with caution by healthcare professionals with adequate training in nutrition support.[30] In a patient with head and neck cancer for instance, low concentrations of serum potassium, magnesium or phosphate may be related to chemotherapy and is unlikely to represent risk of refeeding in the absence of other nutritional risk factors, i.e. prolonged starvation. Conversely normal electrolyte levels should not be interpreted as an indication of low refeeding risk as due to homeostatic mechanisms, serum concentrations of potassium, magnesium and phosphate may be within normal parameters prior to feeding, even in the starved patient. The advice is to commence oral, enteral or parenteral nutrition cautiously, starting at a maximum of 10–20 kcal/kg/day for

high-risk patients and less for severely high-risk patients (5–10 kcal/kg/day).[21, 30] Introduction of nutrition support should be accompanied by vitamin supplementation and monitoring of electrolyte levels, with repletion of electrolytes as necessary.

NUTRITIONAL INTERVENTIONS AND TREATMENT

Surgery

It has long been recognized that surgical outcome, in any speciality, can be robustly linked to the nutritional status of the patient. Malnourished patients have a higher risk of post-operative complications and long-term adverse effects on QOL. In head and neck surgery, post-operative morbidity and mortality is mediated by poor wound healing, higher risk of flap failure, impaired immune function and a general decreased tolerance to stress of major surgery in those who are nutritionally compromised.[5, 31, 32]

Patients requiring surgery for head and neck malignancy will often have advanced disease and require procedures that will, frequently, further interfere with their ability to maintain an adequate oral intake. It is important when counselling patients about their treatment options that surgeons are realistic with them, their families and the allied healthcare professionals in the treating team about potentials for oral intake both immediately after surgery and in the longer term.

Patients need to be fully informed about the effects of surgery on their swallowing. Studies have shown that swallowing consistently remains one of the top priorities for patients following treatment for head and neck cancer.[33] Patients may already have difficulty swallowing due to the site or stage of their tumour. The effect of tumour resection in the oral cavity, oropharynx, hypopharynx and larynx should be explored at pre-treatment assessment by an experienced MDT. Therefore, the patient expectation should be kept realistic and the functional outcomes explained fully in conjunction with the SLT. Options for maintaining nutrition should be discussed in conjunction with a specialist head and neck oncology dietitian and an individualized management plan formed.

For those patients who are malnourished at presentation, early dietetic input is invaluable in the time leading up to surgery. This allows optimization of their nutritional status and early intervention. If patients are clearly unable to meet their nutritional requirements with oral intake due to dysphagia, odynophagia or aspiration, despite optimization of analgesia and SLT input, an early decision regarding enteral nutrition is required to prevent further nutritional decline. Whether this is via a nasogastric tube (NGT) or a gastrostomy tube is a patient-centred decision, based on the following factors: patient preference, tumour stage, the site of the primary tumour (more likely for oral cavity/oropharynx, less likely for larynx), the likely need for post-operative radiotherapy +/– chemotherapy, the predicted length of time to achieve oral intake of a normal consistency or quantity and institutional expertise.[28]

It is imperative to ensure that patients are assessed, advised and monitored up to the point of surgery with respect to their nutritional status. This enables the best possible outcome from surgery in this high-risk group of individuals. Post-operatively, patients should have a form of enteral nutrition available that can be commenced within 24 hours of their surgery.[10] Depending on pre-operative discussions and the nature of surgery, an NGT may be all that is required if early return to oral diet is anticipated. However, if recovery is more likely to be protracted a prophylactic gastrostomy may be more appropriate. If unforeseen complications occur or recovery is slower than anticipated a reactive gastrostomy is also a possibility. In all instances, an appropriate feeding regimen should be prescribed by a specialist head and neck oncology dietitian to stop any delay in post-operative feeding.

Early oral feeding (day 1–7 post-operatively) in primary laryngectomy patients should be considered as studies indicate no evidence of increased fistula rates when compared with standard protocols for commencing oral intake, traditionally > 7 days.[6] Similarly, early oral feeding protocols following oral cavity surgeries are gaining popularity due to evidence suggesting favourable outcomes such as earlier tracheostomy decannulation and reduced length of stay without an increase in morbidity.[34]

Enhanced recovery after surgery (ERAS)

Enhanced recovery programmes have gained popularity over the last 15 years amongst many surgical disciplines. Historically there have been little data pertaining to head and neck surgery, however a consensus based ERAS protocol for the management of patients undergoing head and neck surgery with free flap reconstruction has now been developed.[35]

There are three main aspects of operative care to ERAS:[36]

- **Pre-operative:** assessment, education and counselling about the procedure and its recovery, avoidance of premedication, same day admission/limited hospital stay, attention to fluid balance, minimization of fasting and carbohydrate loading, nutritional optimization.
- **Intra-operative:** minimally invasive surgical techniques, regional anaesthesia, standardized anaesthetic protocol with the use of short-acting anaesthetics, goal-directed fluid therapy, avoidance of drains and high inspired oxygen concentrations.
- **Post-operative:** early mobilization, early removal of drains, catheters and lines, early oral/enteral intake, optimized pain relief, nausea and vomiting prophylaxis and use of prokinetics/laxatives/chewing gum.

The practice of keeping all patients nil by mouth (NBM) from midnight prior to surgery may contribute to an abnormal physiological state thereby slowing down

recovery after major surgery; the abnormal physiology can be further exacerbated by delayed post-operative feeding. In ERAS protocols, patients are not placed NBM from midnight but are given carbohydrate rich fluids up to 2 hours before surgery (carbohydrate loading).

In patients undergoing colorectal surgery it has been demonstrated that pre-operative carbohydrate loading results in shorter hospital stay, less loss of muscle mass and earlier return of bowel function with no increase in risk of aspiration.[37] In some hospitals in the UK, pre-operative carbohydrate loading has been introduced to patients undergoing head and neck surgery with no concerns.[38] Pre-operative carbohydrate loading involves the administration of 100 g of carbohydrate the night before surgery and 50 g carbohydrate up to 2 hours before surgery. Carbohydrate is provided in specialized nutritional supplements. ERAS programmes often recommend commencing nutrition post-operatively within 4 hours of surgery.[39] Current European nutrition guidelines suggest starting enteral feeding within 24 hours.[26]

The mere presence of a pathway with nutrition as an integral part ensures that this is not a neglected facet of peri-operative care. One of the main ways that ERAS is beneficial is by reducing the 'metabolic stress' of major surgery. This manifests as rising levels of insulin resistance post-operatively, related to the magnitude of the operation performed. Insulin resistance lasts for several weeks following surgery and affects all parts of the body's metabolism. There is reduced glucose uptake in body cells leading to loss of lean body mass and reduced muscle function. Pre-operative carbohydrate loading and early post-operative feeding can help reduce the catabolic response to surgery and thus patients recover quicker with fewer complications.[40] Major head and neck surgery does in fact lend itself to many of these general principles of ERAS.[35] Early dietetic assessment, as discussed earlier, and intervention pre-operatively for life-changing surgery is required to ensure realistic outcomes for patients, which is similar to the fundamental principle of ERAS. Most patients can be admitted on the day of surgery. Nutrition is just one part of ERAS pathways. Early mobilization and optimization of post-operative analgesia are also important.

Immunonutrition

Also known as immune enhanced nutrition, immunonutrition is feed containing various additives in the form of amino acids, nucleotides and lipids. Much of the research concentrates on the substances omega 3 (fatty acids from fish oil) with arginine or glutamine.[41] These additional constituents are thought to upregulate the host immune response, modulate the inflammatory response and improve protein synthesis after surgery.[42]

Many randomized controlled trials and several meta analyses have shown that administration of enteral arginine, omega 3 fatty acids and nucleotides reduce infection rate and length of hospital stay in patients with upper or lower gastrointestinal cancer with the greatest benefit seen in malnourished patients.[42]

Arginine alone promotes healing and modulates inflammation and can be used in an enteral feed in isolation. A recent systematic review and meta-analysis showed that the administration of an arginine-enriched feed reduced both the development of fistulas post-operatively as well as the overall length of stay in hospital.[43] Previous studies have also found that arginine may improve fistulas and wound complications in patients with head and neck cancer.[44] Other studies have found similar tendencies with improved wound infection rates but less convincing effects on fistulas.[45]

With the increasing amount of evidence in the literature, post-operative immunonutrition appears to be emerging as another technique in our armamentarium to reduce length of hospital stay. However, the mechanism remains unclear, as other clinical benefits such as reduced complications and infections have not been consistently demonstrated.[10]

CHYLE LEAKS

An uncommon, but major complication of head and neck surgery is a chyle leak or chylous fistula, particularly if surgery involves the left supraclavicular fossa region. The literature suggests an incidence of 0.5–1.4% for thyroidectomy and 2–8% for neck dissection.[46]

Chyle is a by-product of the absorption and digestion of fat. Fat digestion begins in the duodenum with pancreatic lipase, which hydrolyses triglycerides into monoglycerides and free fatty acids. These in turn interact with bile salts and form micelles. The micelles transport the monoglycerides and free fatty acids across the brush border of the villi of the small intestine. Most of the fat absorbed into the epithelial cells combines with cholesterol, phospholipids and lipoproteins to form chylomicrons. These then enter the lacteals of the villi as milky-looking lymphatic fluid (chyle).

The lacteals coalesce to form the cisterna chyli, which traverses the diaphragm to run superiorly as thoracic duct in the posterior thoracic cavity behind with the oesophagus. As the thoracic duct enters the neck it crosses between the internal jugular vein (IJV) and the anterior scalene muscle. It either terminates at the junction of the left IJV and left subclavian vein or drains directly into the IJV. For this reason, the majority of chyle leaks are on the left, although approximately 5% will occur on the right from the right lymphatic duct.[47]

About 2–4 litres of chyle flows through the thoracic duct on a daily basis. Flow rates vary with the amount of dietary fat consumed. Chyle leaks are classified as low output (< 500 mls/24 hours) or high output (> 500 mls/24 hours). Conservative management is appropriate for low-output leaks; high-output ones are more likely to require definitive intervention. Chyle leaks cause local problems with tissue loss and wound healing as well as systemic effects related to fluid loss and electrolyte dysfunction. Early recognition and treatment is essential to reduce morbidity.

The mainstay of all management strategies is nutritionally based. It is based on the theory that reducing

formation of chyle slows down the flow and thus allows the fistula to heal. A triglyceride level >110 mg/dl is diagnostic of a chyle leak. If the triglyceride level is <110 mg/dl further analysis is required to demonstrate the presence of chylomicrons. A triglyceride level <50 mg/dl usually rules out a diagnosis of a chyle leak unless a patient is malnourished or has been fasted.

The principal aims of nutritional management are to reduce the flow of chyle whilst maintaining nutritional status, ensuring adequate fluid balance and replacing electrolyte losses. Normally, when dietary fat is consumed long-chain triglycerides (LCTs) enter the blood-stream via chyle, medium-chain triglycerides (MCTs) are absorbed directly into the portal system. This important differentiation forms the basis on which nutritional management is based. Therefore, the nutritional management is to use a fat-free or high-MCT product. MCT is recommended because it is directly absorbed into the portal system resulting in less chyle production. Many patients with low-output leaks will respond to this intervention alone, thus making early dietetic input essential.[48] To date, no consensus exists on how to nutritionally manage chyle leaks, how long nutrition management should be pursued, or what constitutes an acceptable amount of chyle output. The nutritional intervention is usually dependent on clinician preference.

If dietary manipulation is unsuccessful parenteral nutrition may be required. This should not be used as first line management except in extreme cases, for example, very high volume leaks (>1000 mls). Further alternative treatments include Octreotide, Orlistat or recourse to surgical intervention.

RADIOTHERAPY +/– CHEMOTHERAPY

Patients should be offered pre-treatment assessment before commencing radiotherapy +/– chemotherapy to ensure

- full assessment of baseline nutritional status
- appropriate dietary advice is provided before commencing treatment to correct nutritional deficiencies
- information is provided on the nutritional implications of treatment, including anticipated need for enteral tube feeding support.

It is recognized that radiotherapy can cause side effects that may limit oral intake and lead to weight loss.[11] The addition of chemotherapy during radiotherapy has been shown to lead to increased locoregional control and an 8% improvement in overall survival, but this has been at the cost of increased toxicity.[49] Chemotherapy agents act as radiosensitizers. Unfortunately, the sensitizing effects are not selective for tumour cells and therefore normal tissue in the radiation field is also subject to more toxic radiation. Addition of chemotherapy to radiotherapy schedules is known to significantly increase grade 3 or 4 mucositis in most patients (~88%) compared to only 20–30% of patients treated with radiotherapy alone.[50] Monoclonal antibody treatments (e.g. cetuximab) given in conjunction with radiotherapy will also increase the incidence of mucositis and other toxicities effecting nutritional intake and hence patients should be managed in the same way as for conventional chemoradiotherapy.[10]

The impact of neoadjuvant chemotherapy schedules on nutritional status and oral intake is poorly understood due to limited studies in this area.[10] It is advised that nutritional status is assessed at regular intervals during neoadjuvant chemotherapy cycles to prevent nutritional decline prior to future radiotherapy treatment.

Intensity-modulated radiation therapy (IMRT) is the most commonly used technique to deliver radiotherapy to the tumour and regions at risk. Whilst the benefits of IMRT include the ability to limit radiation toxicity to the salivary glands and critical pharyngeal structures required for swallowing, thus reducing the chronic toxicities of dysphagia and xerostomia, residual toxicity remains with a high rate of weight loss, mucositis and continued need for nutritional support. Independent predictors of severe toxicity with concurrent chemoradiotherapy have been shown to be older age, advanced T stage, primary site in the larynx/pharynx and neck dissection after radiotherapy + chemotherapy.[51]

Radiotherapy side effects start to impact on the patient between the second and third week of treatment with this reaction continuing and increasing during the fourth, fifth and sixth weeks. Side effects peak approximately 1–2 weeks after treatment finishes.[52] Supportive care during chemoradiotherapy is demanding and often requires extensive oral and skin care, opioid medications, antiemetic medications and intensive nutritional support. Chemoradiotherapy can profoundly affect nutritional intake and swallowing physiology thereby causing significant morbidity and diminished QOL.[53] This impairment of oral food and fluid intake as a result of treatment may further exacerbate pre-existing malnutrition.[54]

Ongoing nutritional assessment and counselling by a specialist head and neck oncology dietitian should be part of the patient's treatment plan with patients being reviewed weekly during treatment.[10, 55] Odynophagia and oral pain when eating may lead to a reduction in the types and selection of foods consumed, often at the expense of adequate nutrition. Modifying the texture and consistency of foods is common during treatment. Increasing the frequency of meals and fortifying with nutrient dense foods will minimize nutrient deficiencies by increasing calories and protein. As treatment progresses, many patients will move to pureed or liquid diets and be more reliant on oral nutritional supplements to meet their nutritional requirements. Some patients may require enteral tube feeding to meet their nutritional needs.

Long-term side effects of chemoradiotherapy are more severe than for radiotherapy alone. Dysphagia, pain and dependence on feeding tubes are more common with chemoradiotherapy compared to radiotherapy alone and have negative effects on QOL.[51, 56] Dysphagia usually improves in the first year following treatment but in some cases swallowing dysfunction may be permanent.[57] In addition, the late effects of chemoradiotherapy can include osteoradionecrosis (destruction of bone within the

oral cavity), dental decay, trismus (reduced mouth opening), hearing loss and pharyngeal or oesophageal stenosis. Most late effects of chemoradiotherapy can impact on a patient's ability to eat and drink. It is important to assess nutritional status and oral intake at review appointments even many years after treatment and refer to a specialist head and neck oncology dietitian for advice if oral intake is compromised.

PALLIATIVE CARE

The specialist head and neck oncology dietitian plays a key role in the palliative care team due to the high incidence of weight loss, dysphagia and enteral tube feeding amongst patients with head and neck cancer.[10]

Collaborative assessments and reviews with an SLT can aid in determining the level of nutritional intervention required based upon the nature, severity and likely progression of dysphagia. Although previous goals for maintaining weight and energy intake may no longer be appropriate, patient comfort and QOL should be optimized, for example providing oral or tube feeding to avoid feelings of hunger or thirst during end-of-life care.[9] It is essential that nutritional care is patient-centred, taking into account the holistic needs of the patient whilst being guided by prognosis and medical management.

NUTRITION SUPPORT METHODS

There are three main methods of nutrition support for patients with head and neck cancer. These are oral nutrition support, enteral tube feeding and parenteral nutrition.

The aims of nutrition support are to[58]

- improve the subjective QOL
- enhance anti-tumour treatment effects
- reduce the adverse effects of anti-tumour therapies
- prevent and treat undernutrition.

Oral nutrition support

Healthcare professionals should consider oral nutrition support to improve nutritional intake for people who can swallow safely and are malnourished or at risk of malnutrition.[21] Oral nutrition support involves providing nutrition to improve intake by several methods. These include

- fortifying food with macronutrients including energy, protein and fat as well as vitamins and minerals
- changing the frequency of meals and types of foods consumed
- using oral nutritional supplements.

Previous therapeutic diets, for example, lipid lowering diets, are also often relaxed to prevent further nutritional decline. Oral nutritional supplements are used extensively in patients with head and neck cancer and there are large varieties available. The type used depends on a patient's current nutrition intake, need and preference. The dietitian initiates oral nutritional supplements when there is a deficit in nutritional intake and/or the patient continues to lose weight even when following a high calorie/protein diet.[58]

Enteral tube feeding support

General nutrition support guidelines recommend enteral tube feeding for patients who are malnourished or at risk of malnutrition and have inadequate or unsafe oral intake and a functional gastrointestinal tract.[21] In the post-operative patient, enteral tube feeding is recommended if it is expected that the patient will be unable to eat for more than 5 days post-operatively or unable to maintain at least 50% of recommended intake orally for more than 7 days.[26] In patients undergoing radiotherapy +/– chemotherapy, the benefits of initiating enteral tube feeding when oral intake is inadequate have been demonstrated in terms of improving nutritional intake and minimizing weight loss.[10]

Enteral tube feeding can be delivered via the nose into the stomach or jejunum (nasogastric or nasojejunal tube), or directly into the stomach or jejunum (gastrostomy or jejunostomy tube). **Table 32.4** details the different types of feeding tubes available. The choice of feeding route depends on the expected duration of feeding, site of tumour, treatment plan and intent and patient choice. **Table 32.5** highlights some of the advantages and disadvantages of enteral feeding tubes. In patients with head and neck cancer the preferred route for enteral nutrition is either a nasogastric and/or gastrostomy tube as the stomach is usually accessible. In some circumstances jejunal feeding may be required, for example, patients who have undergone a pharyngolaryngectomy with gastric pullup.

Nasogastric intubation is a procedure involving the insertion of a polyurethane tube (NGT) through the nose, past the throat, down the oesophagus and into the stomach. Tubes are usually placed at bedside but if placement is difficult fluoroscopic or endoscopic placement may be required. There is a risk that the tube can become misplaced into the lungs during insertion, or move out of the stomach at a later stage. It is essential to ensure that the NGT is in the stomach to prevent any complications. pH testing of the NGT aspirate is used as the first-line test method, with pH between 1 and 5.5 indicative of correct

TABLE 32.4 Enteral tube feeding routes and indications

Insertion route	Tube type	Indication
Nose	Nasogastric	Short-term feeding <4 weeks
	Nasojejunal	Short-term feeding when feeding into the stomach is not possible or indicated
Stomach	Gastrostomy	Long-term feeding >4 weeks
Jejunum	Jejunostomy	Long-term feeding when feeding into the stomach is not possible or indicated

TABLE 32.5 Advantages and disadvantages of enteral feeding tubes

Tube type	Advantages	Disadvantages
Nasogastric	• Usually easy to place at bed side • Inexpensive to place • Ideal for short term (< 4 weeks feeding) • Easy to remove when no longer required	• Easy to dislodge • Tube tip position must always be pH checked and a pH of ≤ 5.5. obtained prior to using tube to ensure that tube tip is in stomach • Highly visible • Tubes can block easily with medication due to small diameter of tubes • Laryngeal irritation • Gastro-oesophageal reflux • Nasal sores and erosion • Risk of feeding into the lungs if tube tip position is not in the stomach
Gastrostomy	• Ideal for long-term feeding (>4 weeks) • pH testing not required to check tube tip position as tube tip inserted and secured in stomach • Discrete as located directly in stomach • Unlikely to be dislodged	• Expensive to place compared to NGT insertion • Cannot be placed at bedside • Risk of infection, bleeding and peritonitis from insertion technique • Major complications can impact on ability to deliver oncological treatment
Nasojejunal	• Non-invasive • Ideal for short term (< 4 weeks feeding) • Easy to remove when no longer required • pH checking not required as tube is placed post-pylorically	• Requires placement under X-ray guidance, in interventional radiology or endoscopy • Easy to dislodge • Not feeding into stomach therefore feeding rates are required to be slower due to no gastric reservoir • Feeding times maybe prolonged due to slower feeding rates • Highly visible • Tubes can block easily with medication due to small diameter of tubes and length (> 130 cm) • Laryngeal irritation • Nasal sores and erosion • Potential GI disturbances • With certain medication there is a risk of reduced medication absorption as bypassing stomach
Jejunostomy	• Ideal for providing post-pyloric feeding • Discrete as located directly in jejunum	• Delivery rate of feed less than feeding into stomach due to lack of reservoir • Small diameter of tube increases risk of tube blocking with medication and/or feed • Tube easily dislodged • Requires operation to insert tube

TABLE 32.6 Characteristics of PEG and RIG tubes

Tube type	Characteristics
PEG	• Usually inserted with a 'pull technique'. Tube is pulled through the mouth into gastrointestinal tract endoscopically • Bumper retained • Usually made of polyurethane • Tube must be advanced and rotated at least once a week 2–4 weeks after initial insertion to prevent buried bumper syndrome • Tube life is usually a number of years • Tube is difficult to dislodge
RIG	• Tube usually inserted with a 'push technique'. Tube is inserted directly into the stomach radiologically • Usually balloon retained • Usually made of silicone • Water in balloon must be checked and replaced weekly after the first 1–2 weeks and tube must be rotated • Tube life is usually 3–4 months • Tube may become dislodged if balloon fails

placement in the stomach. A chest X-ray is used only as a second-line test when no aspirate can be obtained or pH indicator paper has failed to confirm the location of the NGT.[59]

There are two main methods of gastrostomy insertion: endoscopic and radiological placement. A gastrostomy that is placed in endoscopy is known as a percutaneous endoscopic gastrostomy (PEG) and one that is placed in radiology is known as a radiologically inserted gastrostomy (RIG). The key characteristics of PEG and RIG tubes are shown in **Table 32.6**. Grant et al.[60] have shown that procedure-related mortality and other complications are higher in patients with head and neck cancer when compared to mixed populations as well as RIG complications being greater than PEG complications. Clinician experience of tube related complications and what services are

available within a head and neck unit generally determine the method of gastrostomy placement.

NGTs are frequently used after surgery as patients often require non-oral feeding for just a few days to weeks. If oral intake is likely to be impaired for longer than 4 weeks after surgery, a patient may have a gastrostomy placed.

For patients with head and neck cancer being treated with chemoradiotherapy, a feeding tube is either placed prior to treatment (prophylactic) or during (reactive). Studies have suggested that a prophylactic gastrostomy leads to improved nutritional outcomes with less weight loss and may improve QOL during and post-treatment compared to reactive NGT.[10] Conversely, prophylactic gastrostomy tubes may have a negative impact on swallow outcomes and lead to tube dependency,[61] though the association of early gastrostomy tube feeding and long-term swallow impairment has been inconclusive.[62, 63] To date there is no consensus on the optimal route (NGT vs gastrostomy) or timing (prophylactic vs reactive) of tube feeding during oncological treatment for head and neck cancer, meaning this is largely determined by clinician and patient preference.[64]

ENTERAL TUBE FEEDING INSERTION CONTRAINDICATIONS

Before inserting any form of enteral feeding tube, the clinical situation, diagnosis, comorbidities, prognosis, possible contraindications, implications for QOL as well as the patient's wishes should all be considered.[64] Both NGT and gastrostomy placement carry risks and in certain situations their placement is contraindicated.

NGT placement may be contraindicated in the following situations:

- severe facial trauma resulting in fractures to the skull base, cribriform plate, and sphenoid sinus, due to the possibility of inserting the tube intracranially[66]
- significant coagulopathy
- oesophagogastric surgery/injury (e.g. gastrectomy/oesophagectomy/oesophageal perforation)
- distal bowel obstruction, perforation or fistula
- competent patient refusal to consent to procedure.

Gastrostomy tube placement may be contraindicated in the following situations:[65]

- significant coagulopathy
- interposed organs (e.g. liver, colon)
- enlarged liver, portal hypertension, confirmed varices and/or ascites
- peritoneal metastasis/carcinoma/dialysis
- peritonitis
- gastroparesis
- gastric outlet obstruction (unless venting gastrostomy indicated)
- small bowel obstruction
- oesophagogastric surgery (e.g. gastrectomy / oesphagectomy)
- hiatus hernia
- acute / uncontrolled psychosis
- advanced dementia
- clearly limited life expectancy
- competent patient refusal to consent to procedure.

The above contraindications may be absolute or relative and their presence makes tube insertion high risk or unfeasible. Specialist input from the MDT (dietitian, gastroenterologist, radiologist and clinical team), should be sought to determine suitability for tube placement where one of more contraindications are identified.

TYPES OF FEED AND DELIVERY METHODS

Dietitians assess the most appropriate type of enteral feed to give patients with head and neck cancer based on their nutritional requirements, their condition, their previous diet, their mobility and lifestyle and their desire to be fed continuously (via a pump) or in smaller volumes (bolus). For patients with head and neck cancer it is usual to use polymeric feeds (whole protein) with or without fibre. Feeds range from 1 kcal/ml to 2.4 kcal/ml with varying levels of protein.

Continuous and bolus feeding

Bolus and continuous feeding are two ways to deliver nutrition to patients who are tube fed. Bolus feeding is defined as the administration of liquid feed (primarily oral nutritional supplements) by syringe or bolus feeding set. A prescribed volume of feed (typically 100–400 ml) is given at regular intervals throughout the day, for example, four times per day. In contrast, continuous feeding involves the administration of a liquid feed via a feeding pump and pump set. The feed is usually run at a set rate, for example, 125 ml/hr for a set period of time; this can be intermittent, for example, overnight feeding, or continuous over 24 hours.

There are advantages and disadvantages of both feeding methods. The choice of feed delivery method is usually determined by patient preference and enteral feed tolerance. In addition, due to the flexible and intermittent nature of bolus feeding, patients with head and neck cancer are generally able to be more mobile with this type of feeding. This is particularly useful if the patient is attending the hospital daily for treatment. Once a patient has completed treatment, bolus feeding may facilitate a quicker transition back to a pre-morbid lifestyle, (returning to work and social activities) as it physiologically mimics a typical eating pattern.

Bolus feeding may be easier to undertake with a gastrostomy tube rather than an NGT as repeated administration of feed boluses requires increased pH testing with a NGT. It can be poorly tolerated by some patients due to

the volume of feed being delivered over a short period of time. In addition, a primary disadvantage of bolus feeding is that it requires manual dexterity and strength. As such this method of feeding may not be suitable for patients with poor manual dexterity, for example, arthritis of the hands. In such instances, continuous feeding using a pump would be the preferred method.

Continuous feeding is often used when commencing patients on enteral tube feeding to assist gastrointestinal tolerance, particularly for patients immediately post head and neck cancer surgery. This is because it allows the lowest possible hourly feed rate to meet nutritional requirements. It is also advantageous if patients are at home and rely on community nursing to administer their enteral feed as it usually requires only two nursing visits a day to set up and disconnect. It is also useful if patients wish to be fed overnight whilst sleeping. A disadvantage of continuous feeding is attachment to the feeding pump. This can lead to decreased mobility, which may affect QOL, however many feed companies provide carry bags to allow portable pump feeding.

Parenteral nutrition support

Parenteral nutrition is rarely required in patients with head and neck cancer as most patients have an accessible and functioning gastrointestinal tract. National data suggests an incidence of <1% for patients with head and neck cancer.[67] Parenteral nutrition may be used as a temporizing measure in patients with head and neck cancer who have obstructive tumours, making placement of an enteral feeding tube impossible. It may also be used for patients who have a chyle leak that has not responded to oral or enteral diet modification. Parenteral nutrition should be considered for individuals who are malnourished or at risk or malnutrition and have inadequate or unsafe oral/enteral nutritional intake and have a non-functional, inaccessible or leaking gastrointestinal tract.[21] Parenteral nutrition can be stopped once adequate oral or enteral nutrition is tolerated and withdrawal should be planned and stepwise with a daily review of the patient's progress.

REHABILITATION

Rehabilitation has been defined as 'the restoration, to the maximum degree possible, of an individual's function and/or role, both mentally and physically, within their family and social networks and within the workplace where appropriate'.[68] Following treatment for head and neck cancer, patients may have long-term side effects of their treatment which affect their ability to eat, drink and communicate. Due to the very nature of multimodality treatment, side effects can vary significantly between patients with regards frequency, timing, severity and impact on QOL.[69] Surgical intervention may permanently alter the texture of diet that a patient can consume and in some instances result in permanent feeding tube dependency. Patients who have had chemoradiotherapy are at high risk of developing both late and long-term side effects such as xerostomia, dysphagia, odynophagia and trismus. One year post-treatment reports suggest that the majority of patients still experience eating problems due to persisting side effects of treatment.[70]

Studies have identified that pain is a significant problem for patients following radical radiotherapy, often leading to a reduction in dietary intake.[71] Patients suffering from reduced laryngeal elevation, reduced cricopharyngeal opening and non-functional swallow on at least one swallow with any bolus type are significantly more likely to require a texture modified diet and have an intake of less than 50% of estimated nutritional requirements.[72] It has been suggested that up to 50% of patients who have undergone head and neck cancer treatment experience dysphagia and up to 60% report severe xerostomia following treatment with an estimated 10% requiring long-term enteral nutrition.[73–75]

Multidisciplinary rehabilitation programmes involving a specialist head and neck dietitian and SLT have the potential to improve outcomes for oral intake. Guidelines recommend that patients with head and neck cancer receive fortnightly reviews by a specialist head and neck dietitian for at least 6 weeks after treatment. In addition, dietetic support should continue for up to 6 months, or for as long as they require management of long-term side effects, weight loss and enteral nutrition.[10] Further research is required to examine the benefits of these proactive rehabilitation programmes in reducing tube dependency in patients with head and neck cancer.

The level and nature of support between patients will vary, as well as being dependent on local resources and guidance. The nutritional status of patients should be closely monitored so that dietary intervention can be adjusted in a timely manner. Locally, support groups such as 'Back to Eating' should be established to provide patients with an encouraging environment to try new foods during the rehabilitation phase. Patients may be discharged by the dietitian once rehabilitation goals have been achieved, however, there should be an agreed process in place to re-access specialist head and neck dietetic services should this be required.[4]

SURVIVORSHIP

As the incidence of cancer increases, alongside recent improvements in cancer treatment, it is expected that patients with head and neck cancer are living well and beyond their cancer diagnosis and treatment.

Ensuring that good survivorship care, incorporating nutrition, is provided to patients with head and neck cancer may lead to a reduction in future mortality by

- reducing the risk of cancer recurrence
- preventing or managing comorbidities such as diabetes, cardiovascular disease and other cancers
- earlier identification of recurrence.

There is limited evidence available detailing specific dietetic support for patients with head and neck cancer in

survivorship as the long-term consequences of treatment are unknown. Patients are encouraged to follow general health promotion recommendations including dietary advice on maintaining a healthy weight (BMI 18.5–25 kg/m^2), limiting alcohol and eating a balanced diet once they have reached a stable weight and are able to meet their nutritional requirements from food. There have been reports that patients with head and neck cancer suffer increased levels of emotional distress, physical limitations, altered body image and relationship difficulties.[76] It is essential that services for survivorship are developed that support and enable them to cope with these needs and allow them to lead a good QOL for as long as possible.

Some patients may continue to require medical led follow-up long term. However, with younger people being diagnosed with head and neck cancer, because of the association of human papillomavirus (HPV) and oropharyngeal cancer, there are a growing number that can be educated and supported to self-manage at home with remote access and timely re-access to clinics.[69] Many survivorship initiatives are recommending structured holistic recovery packages that incorporate the following:

- holistic needs assessment and care planning
- treatment summaries
- health and well-being events
- advice and schemes supporting physical activity.

The specialist head and neck dietitian plays an integral part in the delivery of such survivorship packages by providing nutritional advice tailored to the needs of the patient with head and neck cancer.

CONCLUSION

A specialist head and neck dietitian is an integral part of the head and neck MDT. There is clear evidence to support the benefits of nutrition throughout a patient's head and neck pathway which starts with nutritional screening and pre-treatment optimization. Nearly all patients undergoing treatment will require nutrition support, most commonly oral or enteral tube feeding interventions. The expected impact of treatment on nutrition as well as potential for long-term difficulties with eating and swallowing should be discussed thoroughly at pre-treatment stage. The decision to provide a nutritional intervention such as insertion of a feeding tube should be patient-centred and consider the impact on QOL. It is especially important to consider the individual patient needs for those having primary chemoradiotherapy where optimal route and timing for enteral tube feeding is not certain. Nutrition intervention usually ends in the rehabilitation and survivorship stage of a patient's treatment pathway and more research in this area is required.

KEY POINTS

- A high proportion of patients with head and neck cancer present with malnutrition due to disease site and process, pre-existing dietary issues and psychosocial factors. Identifying malnutrition with a validated screening tool is recommended early in the treatment pathway.
- Nutritional assessment by a specialist head and neck oncology dietitian is advised prior to treatment to allow optimization of nutritional status.
- Pre-operative feeding for 7–14 days should be offered to malnourished patients who are planned for major surgery, even if the surgery must be delayed.
- ERAS protocols in head and neck surgery are likely to improve outcomes and nutritional aspects include prevention of long fasting times pre-operatively, carbohydrate-loading and early enteral and oral feeding post-operatively.
- All patients undergoing (chemo)radiotherapy for head and neck cancer will require weekly nutritional assessment by a specialist dietitian due to the impact of treatment toxicities on swallow and oral intake.
- Nutrition support methods during treatment typically include oral (texture modification, food fortification, nutritional supplements) or enteral tube feeding (reactive or prophylactic via NGT or PEG).
- Following treatment for head and neck cancer, patients are at risk of developing late and long-term side effects, such as xerostomia, dysphagia, odynophagia and trismus which may impact nutritional status.
- Multidisciplinary rehabilitation programmes which include a specialist dietitian and SLT have the potential to improve outcomes for oral intake and facilitate early enteral tube feeding removal.
- It is essential that survivorship services are developed for patients with head and neck cancer as they may suffer increased levels of emotional distress, physical limitations, altered body image and relationship difficulties following treatment.
- Nutritional interventions during palliative care should aim to maximize patient comfort and QOL.

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CHAPTER 34

SPEECH VOICE AND SWALLOW REHABILITATION AFTER CHEMORADIATION

Justin W.G. Roe and Katherine A. Hutcheson

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SEARCH STRATEGY

Data in this chapter may be updated by a Medline search using the keywords: chemoradiation, head and neck cancer, swallowing, voice and functional outcomes.

INTRODUCTION

Radiotherapy for head and neck cancers (HNC) can impart devastating effects on swallowing and communication abilities. Impaired communication and swallowing functions have significant consequences on health and well-being, and limit activities and participation in social situations.

Adverse effects of tumour on swallowing ability prior to treatment are well documented, largely in patients with advanced stage (T3–T4) primary tumours.[1–3] Cancer treatment in most cases, compounds baseline tumour-associated functional deficits. Historically, functional impairments were largely attributed to major surgery. In the last two decades, however, radiotherapy and chemo-radiotherapy regimes have become the main treatment modality to improve locoregional control and offer functional organ preservation for many advanced stage HNC that would have previously required ablative surgery. Despite comparable survival rates after non-surgical organ preservation,[4, 5] it has become increasingly clear that 'organ preservation' does not necessarily result in function preservation, particularly with regard to swallowing mechanics.[6, 7]

Dysphagia is the most commonly cited functional problem after non-surgical organ preservation for HNC, and may ultimately cause aspiration pneumonia, nutritional and hydration compromise, and subsequent reliance on tube feeding. Patients themselves report that swallowing is a top concern before and after treatment with organ-preserving radiotherapy with or without chemotherapy, hereafter referred to as (chemo-)radiotherapy.[8, 9] Speech and voice outcomes are less commonly reported after non-surgical modalities for locoregionally advanced HNC, and pre-treatment data are often lacking in published reports.[10] Nonetheless, recent studies have identified that changes in voice quality are present up to 1 year following organ preservation treatment for HNC,[10] and these changes are also present in those who have been treated for non-laryngeal cancers.[11, 12]

This chapter includes a brief overview of the communication issues experienced by patients with locoregionally advanced HNC treated with non-surgical organ preservation. A review of voice changes after (chemo-)radiotherapy for early glottic cancer is beyond the scope of this chapter. The primary focus of the chapter is an evidence-based review of swallowing outcomes after non-surgical treatment. Swallowing outcomes reported in published literature will be summarized. Predictive factors will be highlighted, in particular, baseline clinical predictors of swallowing. Preventative strategies will be reviewed, including the potential benefits of highly conformal radiation treatment aiming to reduce bystander doses to swallowing-critical structures and swallowing status during radiotherapy. Finally, this chapter will cover the emerging evidence for rehabilitation strategies implemented both prophylactically and following non-surgical treatment for HNC.

COMMUNICATION FOLLOWING CHEMORADIATION FOR HEAD AND NECK CANCER: ASSESSMENT AND MANAGEMENT

Communication outcomes, and in particular voice outcomes, are increasingly relevant in contemporary practice. With changing demographic towards a predominance of HPV-related head and neck disease, patients are now younger at diagnosis with better prognosis for long-term survival. More likely to be employed at diagnosis, impaired communication may well impact on a successful return to work in modern HNC survivors. Organ-sparing chemoradiotherapy preserves, in most cases, the agility of the articulators, and a minimal effect on speech intelligibility should be expected. Nevertheless, both acute and chronic effects of radiotherapy may impart normal tissue effects that cause perceptual differences in speech and voice. Acute toxicities such as ulceration and oral mucositis will impact on comfort when speaking, but resolve in the months following treatment. In addition, radiotherapy fields that include the larynx will inevitably result in voice changes to some extent. Voice is produced by the larynx, which is particularly vulnerable to the effects of radiation. Treatment effects include oedema, fibrosis and hyperemia and erythema.[13] A recent study highlighted that concurrent chemoradiotherapy for non-laryngeal cancers can have a significant, long-term impact on voice production across patient-reported, instrumental and perceptual assessment methods.[11]

A number of assessments are available to assess vocal functioning. Patient reported outcomes can be collected using the Voice-Related Quality of Life (VR-QOL),[14] the Voice Symptom Scale (VoiSS)[15] and the Voice Handicap Index (VHI).[16] Perceptual voice evaluation is usually rated using the GRBAS scale[17] or the CAPE-V. Instrumental evaluation of voice can be conducted for example using laryngeal videostroboscopy. Videostroboscopy assesses symmetry and degree of true vocal fold motion, and vibratory patterns during phonation.

Speech intelligibility is a broader construct of communication, impacted by voice quality, resonance and articulation. A simple, global assessment of intelligibility includes the Understandability of Speech scale as part of the 3-item Performance Status Scale for Head and Neck Cancer.[18] While there are numerous patient reported voice measures, there are few designed specifically for speech. The Speech Handicap Index (SHI) has been validated for use in the HNC population in Dutch and English.[19, 20] Both the VHI and SHI which have been translated and validated for use in a number of languages.[19–21, 27]

Voice therapy after (chemo-)radiotherapy for advanced stage HNC is largely unstudied. Efficacy of behavioural voice therapy has been reported after radiotherapy for early stage glottic cancer,[28] but it is not clear if there is comparable benefit after radiotherapy for advanced HNC. Vocal hygiene (i.e. laryngeal hydration, gentle vocalization) is also empirically recommended to minimize vocal trauma, abuse or maladaptive hyperfunction during the course of radiotherapy and in acute recovery. The role of the speech language pathologists (SLP) during and following radiotherapy is to instruct the patient in vocal hygiene and to prevent maladaptive strategies employed to overcome radiation-induced dysphonia. Following treatment, patients are likely to experience voice difficulties resulting from the oedema and dryness. In the latter stages of treatment and early recovery phase, fundamental frequency be reduced due to greater vocal fold mass and *en bloc* vibratory patterns from bulky, stiff vocal cords. Along with a harsh or rough quality of voice, disturbed frequency of voice contributes to the perceptual changes reported in published studies. Patients may also report vocal fatigue after long periods of talking. Voice problems may persist due to permanent treatment-related changes or vocal abuse resulting from attempts to compensate for transient dysphonia during early recovery.[29]

FUNCTIONAL ASSESSMENT OF SWALLOWING AFTER CHEMORADIOTHERAPY

In recent years, there has been a significant rise in the number of studies reporting swallowing outcomes after organ preservation. To understand the impact of cancer therapy on swallowing function, it is essential that researchers use a range of measures that are sufficiently standardized to allow for future meta-analysis as well as immediate interpretation. One of the challenges in interpreting published data is the heterogeneity of swallowing outcome measures reported in published studies.[30] Much of the radiation oncology literature reports toxicity according to clinician-rated scales such as the Common Terminology Criteria for Adverse Events (CTCAE).[31] While these scales provide invaluable data in relation to a broad range of toxicities, the CTCAE rates dysphagia as function of dietary restrictions, dysphagia symptoms, and enteral/parental nutrition requirements, and lacks sensitivity or specificity to aberrant oropharyngeal swallowing physiology.[6] The broad criteria that define toxicity grades for dysphagia are, unfortunately, not sensitive to physiologic disturbances, asensate dysphagia (e.g. silent aspiration), or specific to pharyngeal dysfunction and downstream effects of dysphagia on quality of life.

Comprehensive dysphagia assessment requires a multidimensional panel of measures, incorporating instrumental examinations of swallowing such as the modified barium swallow (MBS) study (videofluoroscopy) or Fibreoptic Endoscopic Evaluation of Swallowing (FEES), along with clinician-rated and patient-reported outcome measures (PROM). The importance of multidimensional swallowing evaluation has been reinforced by a recent study evaluating swallowing outcomes following radiotherapy. In this longitudinal study of chemoradiotherapy for HNC, it was found that using different methods of swallowing evaluation resulted in complementary, but distinct normal toxicity complication probabilities.[32] The importance of including a broad range of swallowing measures has been further highlighted in the radiation oncology literature with specific guidance to incorporate these multidimensional assessments of swallowing function in Phase III organ preservation trials.[33]

Standardized functional assessments are a critical component of comprehensive clinical care and outcomes research. Functional assessments can include 1) clinician-driven appraisals (e.g. physical examination, instrumental and imaging studies and clinician-rated scales) and 2) patient-reported outcome measures (PROMS) (e.g. quality-of-life questionnaires, symptom inventories). Clinical examinations by speech and language therapists (SLTs – also known as speech language pathologists (SLPs in the USA) include a cranial nerve examination, oral motor assessment, perceptual motor speech and voice ratings, and the clinical examination of the swallow. Observations from these clinical assessment protocols provide the foundation of the functional assessment and offer the advantage of observing speech, voice or swallowing in a more natural environment (e.g. swallowing natural food rather than a contrast agent, or voicing without an endoscope in the mouth or nose), but clinical assessments lack the sensitivity of instrumental studies.

Instrumental examinations and imaging studies are therefore considered the gold-standard because they directly observe the physiology and competency of swallowing, speech or voice production. Instrumental examinations include the MBS study (or videofluoroscopic swallowing study), FEES, and laryngeal videostroboscopy. Indicators of functional status can also be rated as an adjunct to clinical and instrumental studies according to standardized tools such as the Performance Status Scale-Head and Neck (3-items: Normalcy of Diet, Understandability of Speech, Eating in Public), toxicity grading scales European Organization for Research and Treatment of Cancer (EORTC), CTCAE, or simply by record of the presence or absence of gastrostomy or tracheostomy. Functional status scales provide uniform nomenclature for simple, surrogate measures of functioning routinely ascertained in clinical encounters. Each type of functional measure is detailed in the following sections.

Clinical evaluation of swallowing

The importance of the clinical swallowing evaluation is that it provides a baseline on which performance measures can be taken (ideally) before treatment and may predict outcome.[34] A clinical swallowing evaluation is comprised of a number of measures. After completion of a detailed medical history, the clinical examination will include an oromotor evaluation to assess the integrity of the cranial nerves pertaining to swallowing. In addition, swallowing trials will be undertaken to establish the presence of clinical signs of aspiration or overt signs of difficulty. Recent studies have reported on the benefits of the 100 mL Water Swallow Test (WST) as a component of the conventional clinical swallowing evaluation.[35] Offering a low cost quantifiable endpoint from clinical examination, the WST measures swallowing speed, capacity and volume. The WST is easily repeatable at follow-up appointments to monitor changes in swallowing performance. In addition, clinicians can observe for clinical signs of aspiration as is the case in any standard clinical swallowing evaluation. In combination with information gleaned from history taking and oromotor examination, these data signpost referral for a detailed instrumental evaluation of swallowing. The use of a simple, validated tool such as the Performance Status Scale for Head and Neck Cancer (PSS-HN)[36] or Functional Oral Intake Scale (FOIS)[37] should be used in adjunct to the conventional examination to quantify the functional status of the patient with regard to feeding tube dependence and level of oral intake.

Instrumental evaluation of swallowing

A number of instrumental methods are available to examine swallowing function (i.e. physiology, safety or airway protection and efficiency or bolus clearance) in detail. These include solid-state and high-resolution manometry,[37–42] scintigraphy,[43–46] ultrasound,[47–54] transnasal (o)esophagoscopy (TNE),[55, 56] cine magnetic resonance imaging (MRI)[57–59] and advanced computed tomography (CT) techniques.[60, 61] Each of these techniques provides a unique insight into specific features of the deglutition process, however, the most commonly reported technique in the radiation oncology and oropharyngeal dysphagia literature is videofluoroscopy[62] and FEES.[63]

During videofluoroscopy, patients are imaged in lateral and anterior-posterior planes and presented with a range of liquid and food boluses that have been infused with contrast agents, typically barium sulfate. Videofluoroscopic examination of swallowing, commonly referred to as the MBS, allows for visualization and analysis of the oral, pharyngeal and oesophageal stages of the swallow. A number of observations can be made from MBS, including the presence of penetration of material in to the laryngeal airway and tracheal aspiration (quantified per the validated Penetration-Aspiration Scale[64]) and swallowing efficiency (quantified by Oro-Pharyngeal Swallowing Efficiency (OPSE)[45]). More recently the Modified Barium Swallow Impairment Profile (MBSImp) was introduced to comprehensively assess 16 critical components of the oropharyngeal swallow and provide a standardized profile of the physiological swallowing impairment.[45, 65] Based on findings from the MBS, the SLP can establish the nature and extent oropharyngeal dysphagia and develop an individualized rehabilitation plan. Efficacy of tailored swallowing strategies, such as change in posture or modification of the swallowing pattern, can be examined in real-time on the MBS. DIGEST is another method recently developed to measure the severity of pharyngeal stage dysphagia in a manner compatible with CTCAE toxicity grade (1 = mild, 2 = moderate, 3 = severe, 4 = life-threatening/profound) based on the results of the MBS study.[66]

FEES also allows for detailed evaluation of swallowing. While the oral stage cannot be observed and there is white out during the swallow, it provides valuable information on the pharyngeal stage of the swallow and is a useful biofeedback tool, particularly for therapeutic benefit.

Patient-reported outcome measures (PROMS) of swallowing

The patient's perception of their swallowing impairment and how it impacts on their everyday life is arguably a critical outcome of cancer therapy. To that end, PROMs have

gained popularity in recent decades. PROMs complement clinician-rated assessments by quantifying the patient's perceived level of handicap or impairment, and its impact on daily activities and quality of life. More recently, the PROMs have been augmented by carer-reported outcomes to add how dysphagia might impact on quality of life and participation in social situations.[67]

A number of assessments are available that enable clinicians to understand patient's perceived swallowing outcomes following HNC treatment. Specific to HNC, these include, among others, the University of Washington Quality of Life Questionnaire (UW-QOL),[68] the European Organization for Research and Treatment of Cancer (EORTC HN-35),[69] and the MD Anderson Dysphagia Inventory (MDADI).[70] UW-QOL and EORTC are general QOL inventories that include swallowing-specific items, whereas the MDADI is a 20-item inventory focused exclusively on swallowing-related QOL.

The UW-QOL is particularly useful for assessment of multiple domains of functional impairment, and it offers the unique feature of prioritization of key issues for the patient. Research has shown that up to 48% of patients select swallowing as being a priority concern for them 1 year after treatment with 3D-conformal radiotherapy treatment.[8] A recent study of patients treated with parotid-sparing intensity-modulated radiotherapy (IMRT) has found that 40% of patients report swallowing as being a priority concern at 12 months.[9] Popular multi-symptom inventories that include dysphagia symptom items include the MD Anderson Symptom Inventory-Head and Neck module (MDASI-HN)[71] and the Vanderbilt Head and Neck Symptom Scale (VHNSS).[72]

Questionnaires are available to ascertain more details on swallowing-specific quality of life including the MDADI and the SWAL-QOL.[73] Among these, the MDADI was specifically developed and validated for use with HNC patients. Other questionnaires designed to ascertain swallowing symptoms and ability include the EAT-10[74] and the Sydney Swallow Questionnaire (SSQ) that have both been validated for use in HNC.[75] There is consensus that PROMs and clinician-rated measures should be used in concert, because discordance that is recognized between patients' perception of their handicap and clinician-rated observations.

DYSPHAGIA AFTER CHEMORADIOTHERAPY

Outcomes

During (chemo-)radiotherapy, acute damage occurs to the mucosa and soft tissue in the radiation treatment volume leading to an inflammatory reaction and subsequently, mucositis and oedema of the soft tissues.[13, 76, 77] While some improvement of acute symptoms can be expected by 3 months, this is not universal. Persistent, longer-term difficulties have been reported after treatment, months or even years later.[78–81] Commonly reported problems impacting on swallowing safety and efficiency include reduced pharyngeal contraction, reduced base of tongue retraction, incomplete epiglottic deflection, incomplete or delayed laryngeal closure and hyolaryngeal excursion, and abnormal oesophageal opening and stricture.[78, 82–86] While mainly seen in the high dose volume, stricture has been observed in areas that have not been treated in the high dose radiation field, leading authors to suggest that decreased swallowing frequency during treatment may also increase the risk of fibrosis.[83] Jointly, however, current data suggest that aforementioned impairments in laryngopharyngeal physiology are the primary contributors to radiation-associated dysphagia (RAD) rather than stricture. This is particularly the cases for late-RAD, driven often by profoundly impaired pharyngeal propulsion coupled with delayed lower cranial neuropathies.[87] A recent systematic review reported the overall risk of stricture after non-surgical HNC treatment was 7.2% over published series from 1989 to 2008. Interestingly, the rate of stricture was elevated in IMRT series (16.7%) perhaps reflecting intensified regimens of chemoradiation in contemporary organ preservation publications or early methods of IMRT not sufficiently controlling laryngeal and esophageal inlet dose.[88]

A primary observation from instrumental assessment is the presence or absence of aspiration. Penetration of material into the upper airway may be spontaneously cleared by patients, however for some, cumulative penetration or inadequate clearance of airway pharyngeal residue may result in delayed aspiration after the swallow. Aspiration is often silent in upwards of 50% of post-radiotherapy aspirators, and the false negative results of clinical examination in silent aspirators can lead to potentially life threatening aspiration pneumonia. Aspiration is common in patients with HNC. Authors have cited data reporting aspiration rates ranging from 18% to 81% after chemoradiation to all head and neck sites and 18% to 54% in the case of oropharyngeal cancers.[89]

Predictors

Tumour and treatment burden are the most notable clinical predictors of functional outcomes after organ preservation.[90] While data suggest the prognostic significance of the primary and nodal staging per TNM criteria, T-stage appears the most consistent staging variable that impacts the severity of dysphagia, gastrostomy dependence, and aspiration after HNC treatment. Likewise, among sites of HNC treated with radiotherapy or chemoradiotherapy, hypopharyngeal tumours confer the highest risk of developing chronic dysphagia and stricture. Population-level data from the US suggest that patients with oropharyngeal primary tumors have the second highest risk of dysphagia (after hypopharyngeal), followed closely by laryngeal primary tumours.[91] Laryngeal cancers may have performed differently in this study, if small glottis cancers had been stratified out from advanced stage laryngeal cancers that are more likely to manifest dysphagia after treatment.

Treatment intensity significantly impacts functional outcomes. Intensification strategies, whether accelerated fractionation schedules, dose-escalation, or via the addition of systemic agents to radiotherapy regimes, have all been associated with greater toxicity and functional effects in clinical studies. Radiotherapy dose-distribution predicts the degree of swallowing impairment across a variety of

outcome measures.[32] Thus, conformal plans using IMRT have been proposed as a strategy to reduce the burden of dysphagia.[86] It is important to note, however, that swallowing-specific dose-constraints have not historically been included in IMRT algorithms. In fact, unintended elevated bystander doses have been observed in certain swallowing-critical regions of interest including the brainstem, anterior oral cavity (inclusive of critical suprahyoid musculature), and larynx when not optimized in IMRT plans.[92, 93] It follows that the maximal benefit of IMRT on swallowing function may be realized only with swallowing-specific OARs are considered in treatment plans. Significant efforts have been made in the last decade to delineate these regions, and consensus is largely to reduce dose to the pharyngeal constrictor muscle region (particularly SPC) and the larynx , with emerging reports suggesting suprahyoid muscles in the floor of mouth regions as a previously undetected swallowing region of interest.[94–97] Favourable results have also been reported with the sparing of dysphagia-aspiration risk structures (DARS) using IMRT.[89] Given recent reports regarding lower aspiration levels in patients receiving split-field IMRT techniques,[98] potential benefits over whole-field techniques have been discussed in the literature.[94] In addition, de-escalation of total radiotherapy dose is currently proposed in several cooperative group trials in HPV-associated HNC populations who have favourable locoregional control and the potential to live decades with late effects of treatment. Examples of two multicentre studies which have incorporated a dedicated dashboard of multidimentional swallowing measures to explore these areas include the PATHOS and DARS studies.[99, 100]

Likewise, cytotoxic chemotherapy sensitizes tumour and normal tissue to effects of radiotherapy. Thus, treatment intensification by the addition of chemotherapy typically increases swallowing toxicity. Acute and chronic dysphagia is most likely exacerbated when chemotherapy is delivered concurrently with radiotherapy, whereas adverse effects of induction chemotherapy on swallowing function are not established. In fact, induction chemotherapy was found to impart improved local symptoms (diet per PSS-HN, MDADI, and pain scores) prior to definitive local therapy in a trial of oral tongue cancer patients.[101] Favourable long-term swallowing outcomes have also been observed in longitudinal follow-up of patients with locally advanced HNC treated with an induction approach.[102]

Baseline functional status significantly predicts function after treatment. Aspiration, vocal fold paresis, feeding tube dependence and tracheostomy prior to treatment have all been reported as adverse prognostic indicators of functional recovery.[90] That is, organ preservation should not be expected to restore function to the impaired organ. While data suggest that roughly half of patients with vocal fold fixation prior to chemoradiation may recover some mobility, the functional translation of this recovery is not clear.[103, 104] Moreover, aspiration of thin liquids sufficient to necessitate dietary modifications prior to treatment significantly predicts for unsafe oral intake requiring NPO status in long-term survivorship after laryngeal preservation.[85] For these reasons, among others, pre-treatment referral to SLTs for baseline functional assessment has recently been recognized as best practice in patients receiving non-surgical organ preservation by the Triological Society[105] and in the National Institute for Clinical Excellence's Improving Outcomes Guidance for Head and Neck Cancer.[106] It is also a 'top-ten' recommendation from the British Association of Head and Neck Oncologists.[107]

One of the important changes in clinical practice that may contribute to improved swallowing outcomes is the implementation of an individualized approach to tube feeding placement in patients undergoing organ-preserving HNC treatment.[94, 108] As discussed earlier, it is clear that some people may require nutritional support by way of tube feeding simply due to cancer related dysphagia. However, there has been a shift in the clinical practice trends from implementing *prophylactic* gastrostomy feeding in all patients to individualizing decisions on the basis of pre-treatment functioning, nutrition, and tumor burden.[109] Systematic reviews agree that the evidence base regarding optimal tube feeding route is limited at this time.[110] Variation has been reported in approaches to tube feeding in the UK and Australasia.[111, 112] Two primary considerations are timing of placement (prophylactic versus reactive) and the type of tube (nasogastric versus gastrostomy).

Historically, gastrostomy tubes were placed prophylactically in all (or most) patients with locally advanced HNC dispositioned to receive radiotherapy. Recent data, however, suggest that reactive rather than prophylactic feeding tubes are associated with favourable swallowing outcomes and the feasibility of this approach has been established in comprehensive systems that allow for close monitoring of nutrition, hydration and swallowing status during radiotherapy.[113] Rather than placement of prophylactic gastrostomy tubes in patients who may ultimately continue with oral intake during treatment,[114] the use of reactive nasogastric feeding has also been proposed in the literature.[115] Despite more frequent tube displacements, no difference has been reported in patient reported assessments of physical condition or quality of life between those who had nasogastric or gastrostomy feeding.[116]

Prevention and rehabilitation

Improved outcomes in modern trials may be influenced also by more active involvement of rehabilitation professionals such as SLTs and dietitians in recent years. However it is clear from surveys of UK, US and Australasian service delivery that the timing and nature of SLT provision to HNC patients is still variable.[112, 117, 118]

Several studies have examined the potential benefit of prophylactic swallowing therapy for HNC patients, including three randomized clinical studies.[119–121] Proactive swallowing therapy encourages maximal use of the swallowing musculature during radiotherapy. In effort to discourage disuse atrophy, two goals can be outlined in proactive swallowing therapy: eat (that is, continue oral intake during radiotherapy) and exercise (that is, perform targeted swallowing exercise during radiotherapy). Observational data suggest the benefit of maintaining oral intake throughout radiotherapy on long-term diet

outcomes and PROMs.[122, 123] In addition, four institutions have published a range of favourable functional outcomes associated with swallowing exercise during radiotherapy. Prophylactic swallowing exercise has been associated with better swallowing-related quality of life scores,[124, 125] superior base of tongue and epiglottic movement,[126] lower gastrostomy rates,[113] shorter gastrostomy dependence,[113] better post-radiotherapy diet levels[120] and superior muscle composition on post-radiotherapy MRI.[121] Despite many hints of efficacy in these studies, a recent Cochrane review found inconclusive evidence on the benefit of swallowing exercise in this population in large part related to underpowered single institution trials and variable methodology precluding meta-analysis.[128] Data also suggest independent positive associations with both prophylactic swallowing therapy goals: *eat* and *exercise*. That is, patients who both eat and exercise during radiotherapy have the best swallowing outcomes, and patients who either eat or exercise have better swallowing outcomes than those who do neither.[127, 128] Importantly, it has also been raised in the literature that despite fairly uniformly positive findings, studies of proactive swallowing exercise vary in how therapy was delivered and practicalities in individual clinical settings.[94] More recently, there has been interest in the potential of Expiratory Muscle Strength Training (EMST) in the rehabilitation of HNC treatment-related dysphagia. Reduced maximum expiratory pressures have been found in patients with chronic radiation-associated aspiration. Initial findings in the HNC population suggest improved expiratory muscle strength and improved swallowing function following therapy with EMST.[129, 130]

CONCLUSION

In this chapter we have described the impact of disease and treatment effects contributing to communication and swallowing problems following organ preservation protocols for HNC. The SLT is a vital member of the multidisciplinary team. Based on the available evidence, we propose the following key points to optimize functional outcomes.

KEY POINTS

- Refer patients for multidimensional swallowing assessment *before* treatment to tailor proactive swallowing therapy and identify high risk patients.
- Standardize multidimensional swallowing assessments to include clinical swallowing evaluation, instrumental swallowing examination and PROMs.
- Use psychometrically validated, quantitative metrics of swallowing function.
- Implement prophylactic swallowing therapy prior to and during treatment – including targeted swallowing exercise and promotion of oral intake throughout treatment.
- Instruct patients in vocal hygiene during treatment and in the immediate post-treatment phase to prevent secondary voice problems due to vocal hyperfunction.
- Advocate a collaborative approach to care during treatment to minimize side effects such as pain that may impact on the ability to continue swallowing.
- Individualize decisions regarding tube feeding during (chemo-)radiotherapy, with preference towards reactive rather than prophylactic tube placement.
- Establish resources and clinical pathways to work towards tube removal as soon as possible following treatment.
- Implement evidence-based swallowing therapy to address impairments based on instrumental swallowing evaluation.
- Consider highly conformal techniques such as IMRT optimized to spare swallowing critical structures, when possible.
- Consider an individualized approach to treatment de-escalation when possible to reduce toxicity and improve swallowing outcomes.
- Consider the profound effect on health-related quality of life that some HNC survivors may encounter and encourage psychological support to deliver a holistic rehabilitation programme when indicated.
- Ensure systems are in place to monitor and provide interventions for patients with persisting swallowing difficulties after treatment and importantly, late radiation associated dysphagia that can occur even years after functional swallowing.

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CHAPTER 35

SURGICAL ANATOMY OF THE NECK

Laura Warner, Christopher Jennings and John C. Watkinson

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SEARCH STRATEGY

This chapter is a basic science chapter with information from anatomy texts and scientific papers concerning head and neck anatomy, identified through Medline searches. The anatomical evidence is supported by cadaver dissection studies, as well as the medical literature.[1] The clinical evidence is observational.

INTRODUCTION

> 'Anatomy is to physiology as geography is to history; it describes the theatre of events'
>
> Jean Fernel 1497–1558 France.

A sound appreciation of the intricate anatomy of the neck is essential for any surgeon embarking upon operations in the neck. This chapter provides a detailed and clinically focused synopsis of neck anatomy; covering developmental anatomy, surface anatomy and the triangles of the neck, fascial layers, neck musculature and deep neck spaces, as well as the important structures encountered within in the neck such as major blood vessels, lymphatics and important cranial and cervical nerves. Details of the viscera of the neck, such as the larynx, pharynx, oesophagus, trachea, thyroid, parathyroid and salivary glands are discussed elsewhere.

DEVELOPMENTAL ANATOMY

Structures in the neck that are innervated by the cranial nerves are derived from the branchial apparatus. The six branchial arches begin to emerge from 4 weeks' gestation. Each arch has its own cranial nerve, cartilage and artery. The fifth arch obliterates soon after all the branchial arches become apparent. Between the arches sit internal pouches and external clefts or grooves (**Figure 35.1**). The arches, clefts and pouches give the appearance of a series or slit-like grooves, resembling the gills of fish, hence the term 'branchial' which is derived

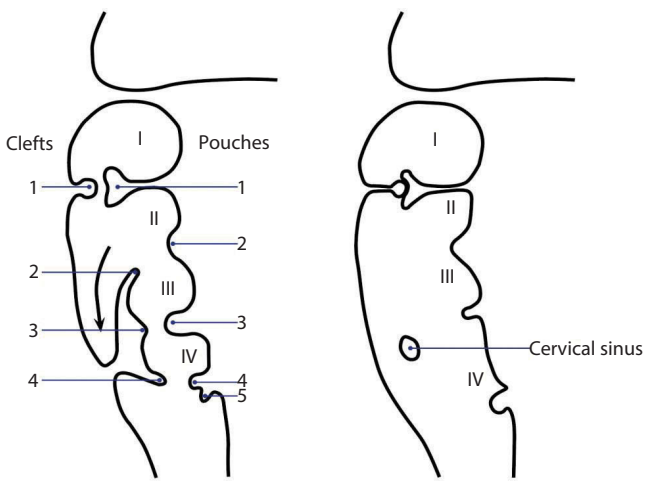


Figure 35.1 Schematic diagram of the branchial apparatus *in utero*.

from the Greek word for gills. The structures derived from the branchial system are outlined in **Table 35.1**.

Congenital abnormalities of the branchial arches can lead to absence or malformation of the head and neck structures arising from the branchial apparatus. This may result in microtia, hearing loss and facial asymmetry and can occur in isolation or as part of a syndrome. Developmental anomalies of the branchial clefts lead to cysts, sinuses or fistulae found in the neck (**Table 35.2**).

First branchial cleft abnormalities are caused by embryonic duplication of the first cleft or first arch and cleft, classified by Work in 1972 into type I and type II respectively.[2] These are rare, representing approximately 5% of branchial cleft anomalies. First branchial cleft abnormalities present as an external fistula tract opening located anterior and inferior to the tragus (type I) or as a fistula tract between an anterior opening close to the angle of the mandible with a posterior opening found in the ear canal or conchal bowl (type II). The fistulae tracts are present from birth and may be asymptomatic or can present with recurrent skin or ear discharge. Treatment is with complete surgical excision of the tract, taking care not to injure the facial nerve. This is particularly relevant with type II lesions which have an inconstant relationship to the facial nerve which may run either deep or superficial to the fistula tract.

Second branchial cleft abnormalities are the most commonly encountered, representing approximately 95% of all

TABLE 35.1 Branchial derivatives

Arch	Nerve	Cartilage	Muscle	Artery	Internal pouch	External cleft
1 Mandibular	Trigeminal (Mandibular branch V3)	Meckel's: Maxilla Malleus Incus	Mylohyoid Anterior digastric Tensor tympani Tensor veli palatini Muscles of mastication	1st aortic arch: maxillary artery	Eustachian tube Middle ear cleft Medial surface of tympanic membrane	External auditory meatus Lateral surface of tympanic membrane
2 Hyoid	Facial	Reichart's: Lesser cornu + upper body of hyoid Stapes superstructure Styloid process	Muscles of facial expression Posterior belly of digastric Platysma Stapedius	2nd aortic arch: stapedial artery	Palatine tonsil	Grows over remaining grooves
3	Glosso-pharyngeal	Greater cornu + lower body of hyoid	Stylopharyngeus Superior & middle constrictor	3rd aortic arch	Inferior parathyroid glands Thymic duct	Obliterated
4	Vagus – Superior laryngeal nerve	Thyroid lamina	Cricothyroid	4th aortic arch: arch of aorta	Superior parathyroid glands	Obliterated
6	Vagus – Recurrent laryngeal nerve	Cricoid Arytenoid cartilages	Inferior constrictor Intrinsic muscles of larynx	6th aortic arch: ductus arteriosus	Ultimobrachial body (forms parafollicular C cells of thyroid)	Obliterated

TABLE 35.2 Congenital branchial abnormalities

Branchial cleft fistula		% of cases	External opening	Internal opening	Associated structures	Symptoms	Management
1st	Work Type I	5%	Anterior and inferior to tragus	External ear canal or middle ear	Lies superficial to facial nerve	Skin or ear discharge	Surgical excision of fistula tract with CN VII monitoring
	Work Type II		Posterior to angle of mandible	Conchal bowl or external ear canal	Inconstant relationship with facial nerve	Skin or ear discharge	Surgical excision of fistula tract with CN VII monitoring
2nd		90%	Anterior border of sternocleidomastoid	Tonsillar fossa	May pass between internal and external carotid artery, runs deep to hypoglossal nerve	Skin discharge associated with upper respiratory tract infections	Surgical excision of fistula tract
3rd and 4th		<5%	Anterior border of sternocleidomastoid muscle, lower neck	Piriform fossa (3rd superior and 4th inferior to superior laryngeal nerve)	4th tract may be associated with thyroid gland	Skin discharge or abscesses, Recurrent thyroiditis (4th)	Surgical excision of tract or endoscopic ablation of internal opening

branchial anomalies. Second cleft fistulae or sinus tracts are found along the anterior border of the sternocleidomastoid muscle, with a tract extending cranially along the carotid sheath which can pass between the internal and external carotid arteries and may run deep to the hypoglossal nerve. The internal opening of a second branchial cleft fistula is found in the tonsillar fossa. Patients present with recurrent skin discharge, often associated with upper respiratory tract infections. Management is with complete surgical excision of the tract, taking care to avoid injury to the carotid arteries or hypoglossal nerve.

Third and fourth branchial cleft abnormalities are rare and are difficult to differentiate clinically so are described together. Third cleft fistulae have a skin opening anterior to the sternocleidomastoid muscle in the lower third of the neck, with an internal opening in the piriform fossa, above the level of the superior laryngeal nerve. Fourth cleft fistulae have similarly located skin openings, however, the internal opening in the piriform fossa is located below the level of the superior laryngeal nerve. Clinical features of third and fourth branchial cleft abnormalities include recurrent skin infections and abscesses. Recurrent thyroiditis is a potential feature of fourth cleft abnormalities as the fistula tract may be closely related to the thyroid gland.[3] Traditional management entails complete excision of the tract, although, more recently, endoscopic ablation of the internal opening within the piriform fossa has been described.[4, 5]

Branchial cysts typically arise from the second branchial cleft, which grows caudally, eventually obliterating the third and fourth clefts in normal development. This creates a potential space known as the cervical sinus, hypothesized to be a site of trapped epithelium which develops into a branchial cleft cyst. Branchial cysts are often asymptomatic and go unnoticed until they enlarge secondary to upper respiratory tract infection. A popular alternative theory for branchial cyst development is cystic degeneration within a lymph node, hypothesized because lymphoid tissue, as well as epithelium, is found within the walls of brachial cysts.[6]

KEY POINTS

- Knowledge of the developmental anatomy is key to understanding neck anatomy.
- Abnormalities of the branchial clefts may present with fistulae, sinuses or cysts.
- Definitive treatment of 1st and 2nd branchial cleft fistulae is complete excision of the tract together with the openings.
- 3rd and 4th branchial cleft abnormalities may be managed with endoscopic ablation of the internal opening.

SURFACE ANATOMY AND TRIANGLES OF THE NECK

Understanding of the surface anatomy of the neck and the structures that can be palpated is essential for surgeons to differentiate pathology from normal anatomy in neck examination. Furthermore, the means to determine the exact location of pathological masses encountered assists with diagnosis. The neck is classically divided into anterior and posterior triangles, which can be further divided into other triangles as described below, helping to compartmentalize the complex anatomy of the neck.

Surface anatomy

The superior border of the neck is defined by the mandible with the deep limits of the floor of mouth anteriorly and skull base posteriorly. The inferior limits of the neck are formed by the upper aspect of the first rib and the first thoracic vertebrae.

MANDIBLE

The lower border of the mandible forms the upper limit of the neck and the division between the neck and the face. The superficial lobe of the submandibular gland is palpable inferior to the lower border of the body of the mandible, just anterior to the angle. The tail of the parotid gland is palpable just posterior to the angle of the mandible.

MASTOID PROCESS

The tip of the mastoid is palpable posterior to the lobule, where the sternocleidomastoid muscle inserts. Anterior and inferior to this the transverse process of the atlas may be palpated.

HYOID BONE

The hyoid is an important bony landmark in the neck. Sitting in the midline of the neck, superior to the thyroid cartilage, the hyoid is a horseshoe-shaped bone with a central body and paired greater and lesser cornus. The greater cornu acts as a guide to the lowermost extent of the marginal mandibular branch of the facial nerve and the level of the hyoid divides nodal levels II and III. The hyoid bone has many muscular attachments; the mylohyoid, geniohyoid and hyoglossus insert onto the superior aspect of the body of the hyoid, whereas the omohyoid, sternohyoid and thyrohyoid muscles insert onto the inferior border. Fibres of the middle constrictor muscles insert into the greater cornu and the stylohyoid ligament attaches to the lesser cornu. Inferiorly the thyrohyoid membrane connects the body of the hyoid to the thyroid cartilage.

Laryngeal cartilages and trachea

The cartilaginous framework of the larynx consists of the thyroid cartilage and cricoid cartilage, which are palpated in the midline of the neck. The arytenoid cartilages lie posteriorly and are not palpable. The thyroid cartilage is shield shaped and is notched superiorly forming a laryngeal prominence that is generally more significant in males than in females. Provided there is no lateral displacement of the larynx the notch can be a helpful surface landmark of the midline of the neck. Inferior to the thyroid cartilage sits the signet ring-shaped cricoid cartilage which is

easily palpable in thin individuals. The cricoid cartilage is at the level of the sixth cervical vertebrae and represents the border between the larynx and trachea, being the first and only complete tracheal ring. It is an important surface landmark to guide placement of the transverse incision used for elective tracheostomy, which is typically between the suprasternal notch and the lower border of the cricoid cartilage in an extended neck.[7] The thyroid and cricoid cartilages are joined by the cricothyroid membrane which is palpable in the midline as an area of cartilage deficiency between the lower border of the thyroid cartilage and the cricoid. This membrane forms an important landmark for emergency front of neck access as it is a relatively avascular plane where temporary airway access can be gained via needle or scalpel cricothyroidotomy. Inferior to the cricoid the cartilaginous rings of the cervical trachea can be palpated.

Thyroid

The isthmus of the thyroid gland can be palpated overlying the second and third tracheal rings. The lobes of the thyroid are located deep to the lower third of the sternocleidomastoid muscles and are not palpable unless enlarged.

Sternocleidomastoid muscle

The sternocleidomastoid muscle has a sternal head which arises from the manubrium and a fan-shaped clavicular head that arises from the medial part of the clavicle. The sternocleidomastoid divides the neck into anterior and posterior triangles, as outlined below. The carotid sheath runs deep to the sternocleidomastoid muscle, the bulk of the muscle provides a degree of protection to the major vessels from penetrating neck injuries. The lymph nodes of the jugular chains are located deep to the muscle. Turning the patient's head towards the side of the neck being palpated relaxes the muscle to allow palpation of the deeper lymph nodes.

Trapezius muscle

The trapezius forms the posterior border of the posterior triangle and the posterior limit of the nodal basins of the neck. Posterior to the trapezius lies the para-spinal musculature and the vertebrae.

Marginal mandibular branch of the facial nerve

The path of the marginal mandibular nerve is important to consider during many neck procedures to avoid inadvertent injury. It originates from the lower division of the facial nerve after the stylomastoid foramen and courses anteriorly and inferiorly from the lower aspect of the parotid gland, extending to the level of the greater cornu of the hyoid at its lowest point.[8] Whilst the exact course of the nerve and number and location of branches may be variable, it is reliably located at the point where it crosses the mandible to leave the neck, running with the facial artery, from which a palpable pulse may be located just anterior to the angle of the mandible. Incisions should be placed below the level of greater cornu of the hyoid, typically two finger breaths below the lower border of the mandible, to avoid injury to the nerve. Many surgical strategies exist to avoid inadvertent injury during neck dissection. Some surgeons advocate raising the flap in the immediate subplatysmal plane and locating the nerve before incising fascia inferior to it to retract the nerve above the level of the mandible, some suggest ligating the facial vein inferior to the lower border of the submandibular gland and retracting the vein and fascia upwards to protect the nerve as the marginal mandibular nerve is reliably located superficially to the facial vessels.

Spinal accessory nerve

The course of spinal accessory nerve is important to appreciate as it can be accidentally injured in procedures in both the anterior and posterior triangles of the neck. After exiting the skull via the jugular foramen, the spinal accessory nerve courses inferiorly and laterally in the neck to provide motor supply to the sternocleidomastoid muscle, which it passes through, and the trapezius. The nerve can be reliably located over the transverse process of the atlas, palpable anterior and inferior to the mastoid tip. It then enters the sternocleidomastoid muscle, typically at the junction of the superior and middle thirds and exits the posterior border of the sternocleidomastoid 1 cm above Erb's point where the cervical plexus nerves emerge from the posterior border of the muscle.[9] The accessory nerve then follows a variable course across the posterior triangle to enter the trapezius muscle at the junction of its middle and lower thirds. The spinal accessory nerve is an important landmark in sub-dividing lymph node levels IIa and IIb.

Carotid artery

The pulse of the carotid artery is most easily palpated at the level of the carotid bifurcation, located between the angle of the mandible and greater cornu of the hyoid, found at the anterior border of the sternocleidomastoid muscle.

Jugular veins

The internal jugular vein (IJV) runs with the carotid artery and vagus nerve in the carotid sheath. The surface marking of the IJV is parallel and slightly lateral to the common carotid artery. The external jugular vein is often visible, running inferior from the angle of the mandible, crossing at the mid-point of the sternocleidomastoid muscle and extending deep to the posterior border of the clavicular head of sternocleidomastoid to meet the internal jugular and anterior jugular veins. The anterior jugular veins run para-midline, superficial to the sternohyoid and thyrohyoid muscles.

Root of the neck

The root of the neck is defined by the manubrium, the sternoclavicular joints and the clavicles, which articulate with the acromion laterally. Above the sternal notch is the suprasternal fossa, also known as Burns space.[10] Chassaignac's triangle (**Figure 35.2**) is the space between the longus colli muscle, the anterior scalene muscle as it attaches to the C6 tubercle (Chassaignac's tubercle) with the subclavian vein as the inferior border. The scalene lymph nodes are located in this space, which should be explored during neck dissection. Lymphadenopathy in this location frequently represents metastasis either from the thyroid or from a primary site below the clavicles which may be of breast, lung, stomach or ovarian origin. The thoracic duct is encountered here, either on the left as a main trunk, or as a network of smaller lymphatic channels on either side. Care must be taken to avoid injury to these vessels to avoid chylous fluid leak during neck dissection.

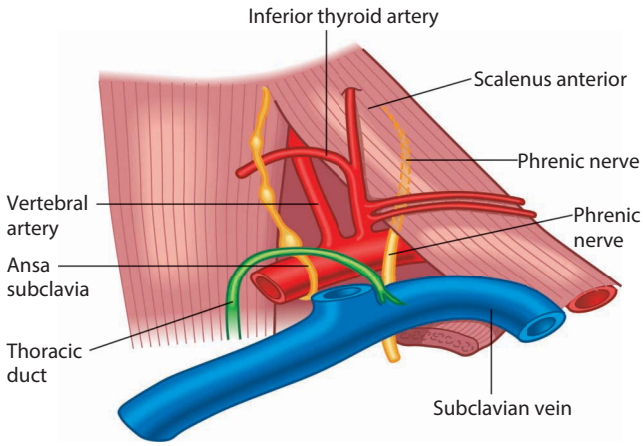


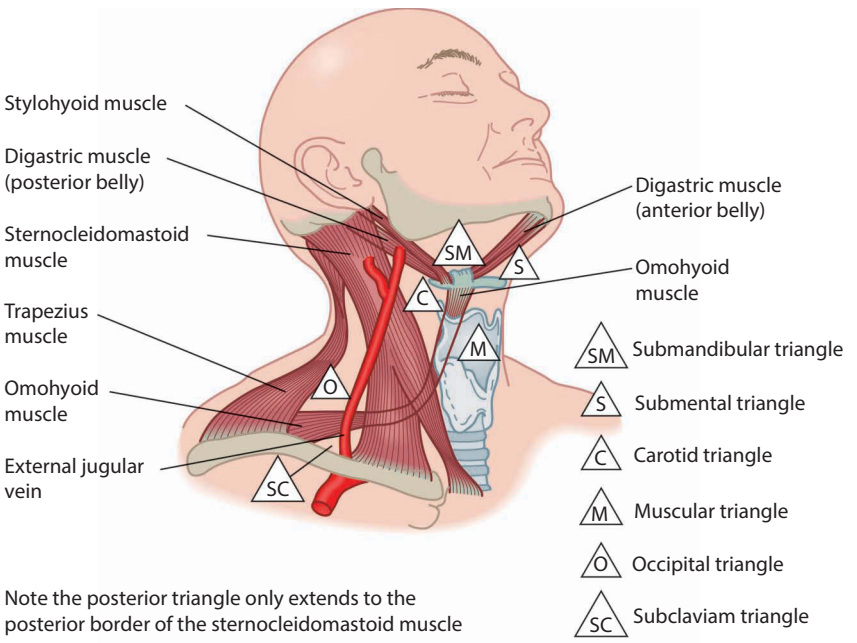
Figure 35.2 Chassaignac's triangle.

KEY POINTS

- Surface anatomy of nerves and vessels must be considered when planning incisions.
- The marginal mandibular branch of the facial nerve can run as low in the neck as the greater cornu of the hyoid; incisions should be placed below this level to avoid injury to both this nerve and the cervical branch of the facial nerve.
- The spinal accessory nerve runs in the roof of the posterior triangle; all important structures lie caudal to the nerve.

Triangles of the neck

The neck is classically divided into anterior and posterior triangles (**Figure 35.3**), by the posterior border of the sternocleidomastoid muscle. These triangles can be further sub-divided into distinct anatomical triangles known as the submental, submandibular, carotid, muscular and subclavian triangles.



Occipital triangle + Subclavian triangle } Posterior triangle

Submental triangle + Submandibular triangle + Carotid triangle + Muscular triangle } Anterior triangle

Figure 35.3 Triangles of the neck.

TABLE 35.3 Summary of the contents of the anterior triangle

Muscles	Vessels	Nerves	Viscera	Other
Digastric	External carotid artery and branches (except posterior auricular)	Internal and external laryngeal nerves	Thyroid and larynx	Jugular chain of lymph nodes
Stylohyoid and mylohyoid	Internal and anterior jugular vein and tributaries	Nerve to mylohyoid	Submental and submandibular glands	
Superior belly of the omohyoid		Hypoglossal nerve		
Strap muscles				

ANTERIOR TRIANGLE

The anterior triangle is defined by the midline anteriorly, the inferior border of the body of the mandible superiorly and the posterior border of sternocleidomastoid. The majority of the anatomical structures of the neck of importance to the head and neck surgeon are found within the anterior triangle, as summarized in **Table 35.3**. The anterior triangle is further divided into the submental, submandibular, carotid and muscular triangles.

SUBMENTAL TRIANGLE

The submental triangle is a single midline triangle located inferior to the mental process of the mandible in the upper neck, as opposed to the other triangles which are paired on each side of the neck. The boundaries are the anterior bellies of digastric laterally and the body of the hyoid bone inferiorly. The mylohyoid muscle forms the floor of the triangle. The contents include fatty tissue, level Ia lymph nodes and small veins that drain into the anterior jugular veins.

SUBMANDIBULAR TRIANGLE

The submandibular triangle (**Figure 35.4**) is also known as the digastric triangle as it lies between the anterior belly of digastric, which forms its anterior limit and the posterior belly of digastric which acts as the infero-lateral border with the stylohyoid muscle. The superior limit is formed by the inferior border of the body of the mandible. The floor is formed by the mylohyoid muscle anteriorly and the hyoglossus posteriorly. The submandibular triangle contains many important anatomical structures including the facial artery and veins, the marginal mandibular branch of the facial nerve, the submandibular salivary gland and lymph nodes of level Ib.

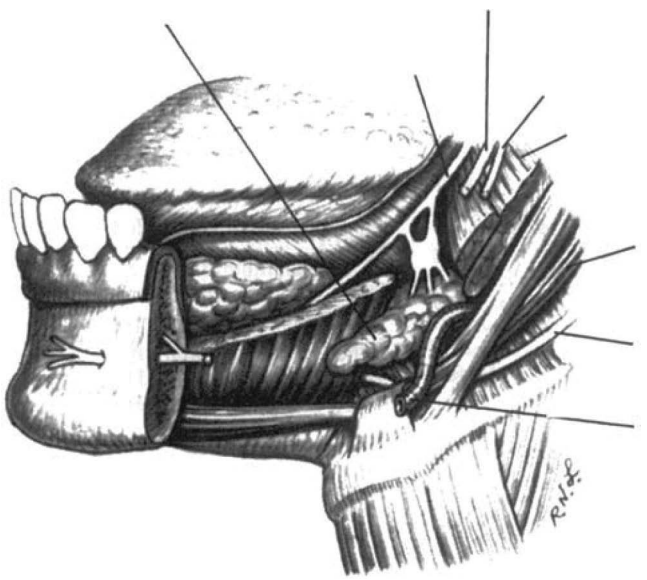


Figure 35.4 Submandibular triangle.

CAROTID TRIANGLE

The carotid triangle is bounded by the posterior border of sternocleidomastoid muscle laterally, the posterior belly of digastric superiorly and the superior belly of omohyoid medially. The contents include the superior part of the carotid sheath, containing the common carotid artery, the carotid bifurcation and the internal and external carotid arteries. The proximal superior thyroid artery, ascending pharyngeal artery, lingual artery, facial artery and occasionally the occipital artery may be found in this triangle. The corresponding veins drain into the jugular vein within the carotid triangle. The vagus nerve, running deep to the vessels in the carotid sheath, the hypoglossal nerve, the superior root of the ansa cervicalis, the superior laryngeal nerve branching from the vagus nerve are all found within the carotid triangle, with lymph nodes of the jugular chain.

MUSCULAR TRIANGLE

The muscular triangle is defined by the lower posterior border of the sternocleidomastoid muscle infero-laterally, the superior belly of omohyoid supero-laterally and the midline. The contents include the lower part of the carotid sheath, the sternohyoid and thyrohyoid muscles, the thyroid and parathyroid glands and the upper aerodigestive tract.

POSTERIOR TRIANGLE

The posterior triangle is bounded by the posterior border of the sternocleidomastoid muscle anteriorly, the anterior border of the trapezius posteriorly and the clavicle inferiorly. The floor is formed by the splenius capitus, levator scapulae and the posterior, middle and

TABLE 35.4 Summary of the contents of the posterior triangle

Muscles	Vessels	Nerves	Other
Omohyoid	Occipital, transverse cervical, suprascapular and subclavian arteries	Cervical and brachial plexus	Lymph nodes
	Transverse cervical, suprascapular and external jugular veins		

anterior scalene muscles respectively from superior to inferior. These muscles are covered by prevertebral fascia and represent the deep limit of resection during neck dissection procedures. The accessory nerve runs across the roof of the posterior triangle, with all other important anatomical structures and lymph nodes positioned caudal to it. Posterior to the trapezius muscle is the cervico-occipital area which contains paraspinal musculature, without lymph nodes or any other anatomical structures of relevance in head and neck surgery. The contents of the posterior triangle are summarized in **Table 35.4**.

SUBCLAVIAN TRIANGLE

The boundaries of the subclavian triangle are the inferior belly of the omohyoid, the clavicle and the posterior border of the sternocleidomastoid muscle. It contains the branchial plexus, emerging between the anterior and middle scalene muscles, the transverse cervical artery and suprascapular artery, which are branches of the thyrocervical trunk. The domes of the pleura with the overlying supra-pleural fascia and the subclavian artery and vein are also found within the subclavian triangle so care must be taken not to injure these structures during neck dissection if retro-clavicular dissection is necessary.

KEY POINTS

- The anatomical triangles of the neck help to compartmentalize the anatomy of the neck.
- The travel from one triangle to another facilitates the concept of neck dissection.
- Sound knowledge of both triangles and contents converts two-dimensional knowledge into three-dimensional surgical reality.

SKIN

Skin of the neck

The relaxed skin tension lines of the neck (**Figure 35.5**) run perpendicular to the fibres of the underlying platysma. These lines create skin creases that run transversely when the skin is not under tension.[11] Wherever possible, surgical incisions should be placed within these skin creases to create cosmetically acceptable surgical scars.

Vascular supply of the skin

The blood supply to the neck skin is derived from branches of the facial, posterior auricular, occipital and subclavian arteries. These arteries, with accompanying veins, form a network within the platysma muscle that supplies the overlying subdermal plexus, from which the overlying skin draws its blood supply. This is an important point to consider during neck surgery as skin flaps should be raised in the subplatysmal plane to preserve the blood supply to the skin, thereby avoiding skin necrosis.

The anterior cervical skin is supplied by branches of the superior thyroid artery and the transverse cervical artery. The posterior cervical skin is supplied by branches of the occipital artery and the deep cervical branches from the costocervical trunk. The superior neck skin derives its blood supply from the occipital artery through its branch to the sternocleidomastoid, the superior fibres of which insert into the upper neck skin. The submental and submandibular branches of the facial artery supply the anterior upper neck. The transverse cervical and suprascapular

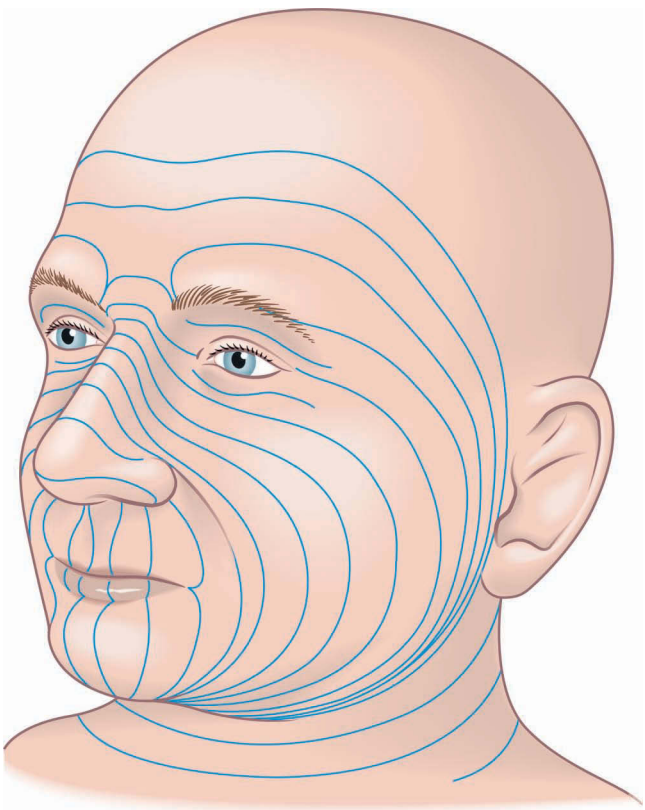


Figure 35.5 Relaxed skin tension lines.

branches of the subclavian artery via the thyrocervical trunk supply the skin of the inferior neck. The venous drainage follows the arterial supply, ultimately draining into the internal and external jugular veins.

Lymphatic drainage of the skin of the neck

In general, the lymphatic drainage of the skin drains into the superficial cervical lymph nodes in closest proximity, with division between anterior and posterior neck zones (**Figure 35.6**). The occipital, post-auricular, supraclavicular and posterior triangle lymph nodes drain the posterior head and neck, including the scalp, whereas the neck skin areas drain into the anterior nodal groups.[12] The anterior neck skin inferior to the hyoid bone drains into the lymph nodes related to the anterior jugular vein, which then drain into the deep cervical chain. The skin above the hyoid bone drains superiorly into the submental and submandibular lymph nodes. Parotid lymph nodes are a common site for occult nodal involvement in skin cancers so parotidectomy should be considered for any neck dissection procedure for skin cancer.

KEY POINTS

- Skin incisions placed within relaxed skin tension lines leave cosmetically acceptable scars.
- Skin flaps should be raised in the subplatysmal plane to avoid skin necrosis.
- Lymphatic drainage of the skin is to the closest superficial nodes; anterior neck and facial skin drains to anterior nodal zones and posterior lymphatics drain posterior neck and scalp.
- The parotid lymph nodes are a frequent site for metastasis from head and neck skin malignancy.
- Skin flap movement is facilitated by elastic properties; these are affected by age, sun exposure and smoking, as well as the presence of infection or previous radiotherapy.

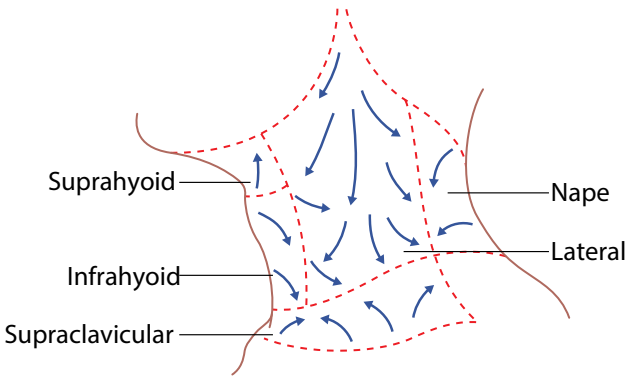


Figure 35.6 Lymphatic drainage of the skin of the neck. The lymphatics of the skin in the suprahyoid region drain to level I, the submental and submandibular lymph nodes. The lymphatics of the skin of the rest of the neck drain to levels II, III and IV, apart from the posterior lateral neck skin lymphatics which drain into the spinal accessory nodes in the posterior triangle.[13]

FASCIAL LAYERS

The neck has superficial and deep fascial planes which encase the structures of the neck (**Figure 35.7**). The deep fascial layer has three distinct layers; the superficial investing layer, the visceral layer and the deep layer. An understanding of the fascial planes of the neck assists in neck surgery as identification of the fascia allows dissection within a safe and relatively bloodless plane.

Superficial cervical fascia

This thin layer of fascia invests the platysma muscle and is penetrated by small vessels supplying the skin, therefore skin flaps are raised in the subplatysmal plane to preserve the blood supply to the skin, as mentioned previously. Inferiorly this creates an aponeurosis that either attaches to skin of the neck or continues inferiorly, becoming continuous with the fascia of the deltoid and pectoralis major muscles.

Deep cervical fascia

INVESTING LAYER

The superficial layer of the deep cervical fascia, also known as the investing layer, forms a fascial cylinder that contains most of the structures of the neck, including all of the nodal stations. Arising from the ligamentum nuchae and the spinous process of the cervical vertebrae posteriorly this layer invests the entire neck, dividing to enclose the sternocleidomastoid, omohyoid, infrahyoid and trapezius muscles. The investing fascia attaches superiorly at the superior nuchal lines and to the mastoid tip and zygoma. The fascia splits to enclose the parotid gland as the parotid fascia, the deep layer of which fuses with the fascia of the internal carotid artery (ICA). Anteriorly the investing layer of fascia attaches to the hyoid bone and to the acromion, clavicle and sternum inferiorly.

CAROTID SHEATH

The carotid sheath is derived from the investing layer of deep cervical fascia, medial to the sternocleidomastoid muscle. It encloses the common carotid artery and the internal and external carotid arteries after the bifurcation, the IJV and the vagus nerve. It is thicker around the arteries, but loose around the IJV allowing expansion during times of increased venous flow. The carotid sheath is connected to other fascial layers by loose areolar tissue.

PRETRACHEAL FASCIA

This middle layer of the deep cervical fascia, known as the pretracheal or visceral layer of cervical fascia, is again derived from the investing layer. It attaches to the hyoid bone superiorly and can be considered as having two parts: the muscular compartment encasing the infrahyoid

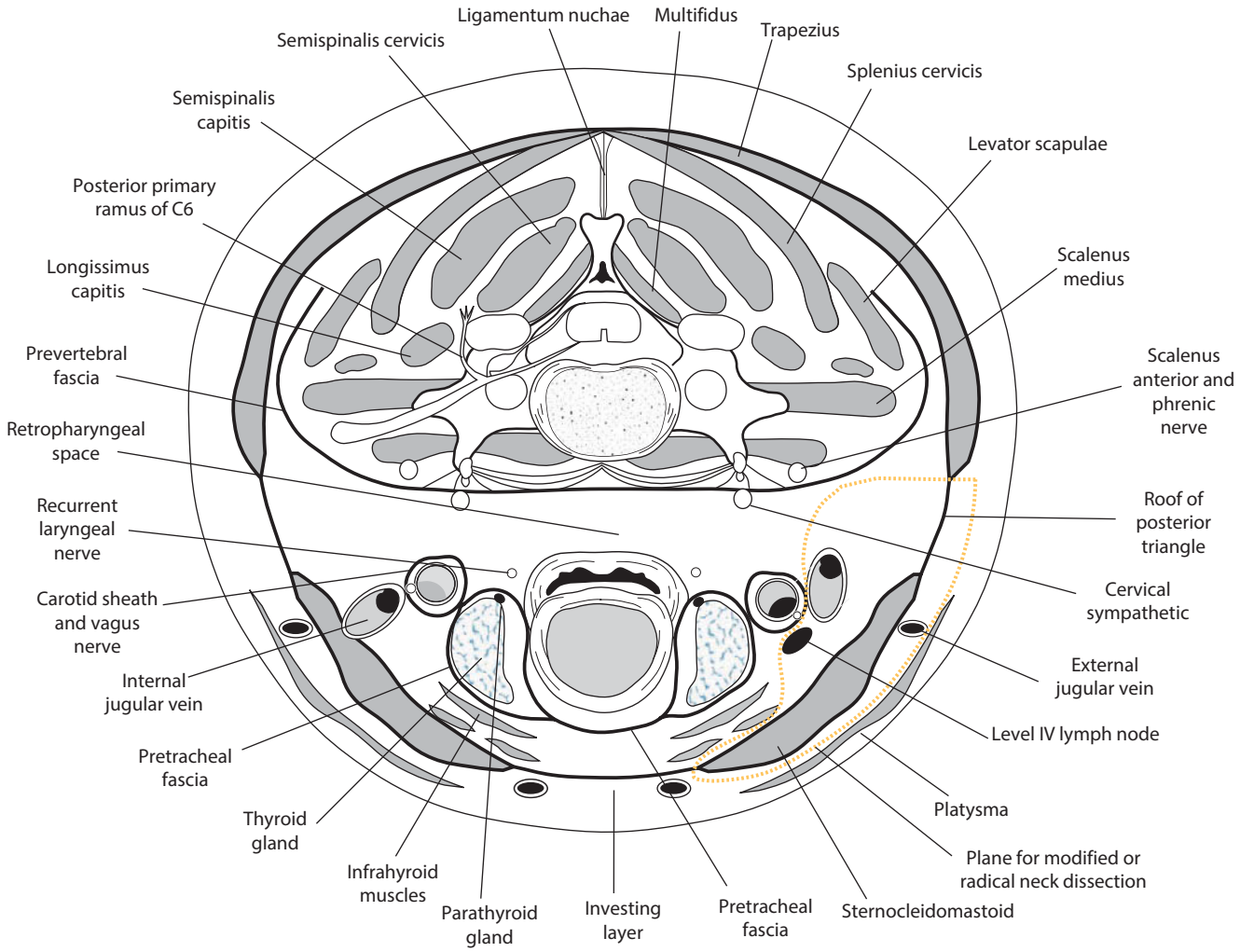


Figure 35.7 Fascial layers of the neck.

muscles and the visceral compartment containing the trachea, the thyroid gland, the pharynx and upper oesophagus. Inferiorly it fuses with the fascia of the superior mediastinum around the great vessels and the fibrous pericardium. Laterally it connects to the carotid sheath by loose areolar tissue.

PREVERTEBRAL FASCIA

The deepest layer of cervical fascia is also known as the prevertebral fascia as it encompasses the posterior neck muscles, the scalene muscles and the vertebrae. It forms the floor of the posterior triangle and represents the deep limit of neck dissection and the plane between the cervical vertebrae and the upper aerodigestive tract, allowing the pharynx to move freely during deglutition. The alar fascia is a supplementary layer of fascia anterior to the prevertebral fascia, extending from the skull base to the posterior mediastinum to the level of the second thoracic vertebra. The danger space, described in 'Retropharyngeal space' below, lies between the prevertebral fascia and the alar fascia.

KEY POINTS

- The fascial planes of the neck form dissection tunnels which can be followed to surgically unlock the neck.
- The investing layer of deep cervical fascia encases all of the nodal zones of the neck.
- The prevertebral fascia is the deep margin of neck dissection surgery, protecting the phrenic nerve and branchial plexus which run deep to the fascia.
- Access and definitive surgery through the fascial planes of neck is best facilitated with tissues under tension and sharp dissection.

NECK SPACES

Between the fascial layers of the neck are several anatomical compartments, containing only loose areolar tissue in healthy subjects. Whilst fascial layers limit the spread of infection, these inter-connected spaces can act as routes of transmission of infection or neoplasia.

Submental space

The borders of the submental space correspond to the submental triangle, as described above, with a superficial limit of superficial cervical fascia and the deep limit of the mylohyoid and geniohyoid muscles. The lymph nodes of level Ia are found within this space.

Submandibular space

The submandibular space is of key clinical significance as it is a route of spread of infection between the neck and floor of mouth. The superior limit of the submandibular space is the mucosa of the floor of the mouth, inferiorly it is defined by the investing layer of deep cervical fascia from the mandible and the hyoid bone. The anterior and posterior bellies of the digastric muscle form the antero-inferior and postero-inferior boundaries respectively. The superficial limit of this space is the investing layer of deep cervical fascia which wraps around the submandibular gland, forming a tough membrane that supports the gland. The mylohyoid muscle runs through the middle of the submandibular space, dividing it into superior and inferior compartments, which communicate around the free posterior edge of mylohyoid.[14] The superior space, also termed the sublingual space, contains the sublingual gland, the deep portion of the submandibular gland and the lingual nerve. The inferior space holds the superficial lobe of the submandibular gland. Both areas contain lymph nodes and branches of the facial vessels.

Between the submandibular gland and the mylohyoid muscle is the loose and distensible epimysium. The deep fascia does not split to enclose the submandibular gland so swelling in this space is limited by the attachments of the mylohyoid muscle and deep fascia. Subsequently distension of this space occurs in a cephalic and medial direction.[15] Ludwig's angina is a life-threatening airway complication of submandibular space infection, characterized by rapid onset of cellulitis of the floor of mouth tissues, causing swelling, induration and tongue elevation resulting in a compromised airway. Submandibular space infections are most commonly odontogenic in origin but can occur secondary to submandibular sialadenitis, lymphadenitis, trauma or after surgery.

Peritonsillar space

The potential space between the palatine tonsil and the superior constrictor muscle is known as the peritonsillar space. The condensation of the pharyngobasillar which forms the tonsillar capsule may be breached by bacterial infections of the tonsil, resulting in abscess formation in the peritonsillar space, also known as a quinsy. Untreated peritonsillar infections may spread to involve the parapharyngeal space.

Parapharyngeal space

The parapharyngeal space (**Figure 35.8**) is an inverted pyramid-shaped space, extending from the petrous temporal bone superiorly to the level of the hyoid. The space is bounded by the superior constrictor muscle medially and the pterygoid muscles, the parotid salivary gland and the mandible laterally. The styloid process and its attachments pass through the space, dividing it into pre-styloid and post-styloid compartments.

The pre-styloid compartment contains fat, connective tissue, the maxillary artery, the inferior alveolar nerve, the lingual nerve and the auriculotemporal nerve. The post-styloid compartment contains the carotid sheath and its contents, the glossopharyngeal and hypoglossal nerves, the sympathetic chain and lymph nodes. The determination between pre- and post-styloid involvement and displacement of the parapharyngeal fat pad are key radiological features which aid in diagnosis of parapharyngeal

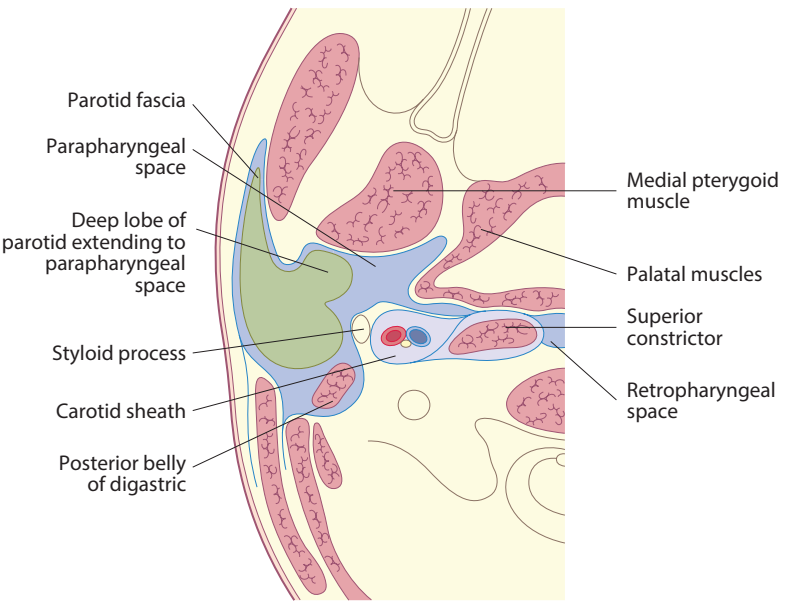


Figure 35.8 Parapharyngeal space.

space neoplasia. Pre-styloid lesions are most commonly associated with the deep lobe of the parotid gland and will deflect the carotid sheath and parapharyngeal fat posteromedially. Lesions in the post-styloid compartment are frequently of neuroendocrine origin, arising from the carotid sheath as carotid body tumours or vagal schwannomas, or neuromas of the sympathetic chain. Post-styloid lesions displace the parapharyngeal fat pad anteriorly. Surgical access to the parapharyngeal space can be challenging and may require mobilization of the parotid gland or lip split mandibulotomy.

The parapharyngeal space is a central connection for other deep neck spaces and as a result is a common site for deep neck abscess formation.[16, 17] Abscesses of the parapharyngeal space may occur because of spread from the submandibular space secondary to oro-dental causes, or from the peritonsillar space. Parapharyngeal space abscesses readily result in airway compromise if untreated. Medial displacement of the tonsil and lateral oropharyngeal wall will be seen but neck swelling or asymmetry may or may not be present. Trismus may also occur secondary to inflammation of the pterygoid muscles. The two parapharyngeal spaces communicate with the retropharyngeal space posteriorly and infection may readily spread into this compartment.

Retropharyngeal space

Between the two parapharyngeal spaces is the retropharyngeal space which is continuous with both. The superior limit of the retropharyngeal space is the skull base and it is continuous inferiorly with the posterior mediastinum, down to the level of the carina. The anterior boundary in the neck is the buccopharyngeal fascia which encases the pharyngeal constrictors, the posterior limit is the alar fascial component of the prevertebral fascia. The only contents of this space are the retropharyngeal lymph nodes, which typically regress by adulthood but can represent a route of metastatic nodal spread from midline or posterior tumours of the pharynx. Radiological evidence of retropharyngeal lymphadenopathy in adults should therefore raise the suspicion of head and neck malignancy.

Infection of the retropharyngeal space may occur indirectly, tracking from the parapharyngeal space or directly secondary to perforation of the pharynx or cervical oesophagus. Retropharyngeal abscesses are more commonly seen in children than in adults, secondary to bacterial infection of the upper aerodigestive tract and may result in airway obstruction due to anterior displacement of the airway.

The alar space, known colloquially as the 'danger space' is a further potential space located posterior to the retropharyngeal space, between the alar fascial component of the prevertebral fascia and the prevertebral fascia itself, extending to the level of the diaphragm. This space is only visible radiologically if distended due to collection within this area. The name 'danger space' refers to the potential for neck infections to readily spread into the thorax and cause mediastinitis.

Prevertebral space

The prevertebral space is the potential area posterior to the prevertebral fascia and anterior to the vertebral column and para-spinal musculature. Spread of infection to this area may occur as a result of traumatic perforation of the pharynx or oesophagus, or because of a breach of prevertebral fascia from retropharyngeal infection. Infection in the prevertebral space can cause spinal osteomyelitis and spinal cord compression. Prevertebral space invasion in head and neck malignancy is a feature which often signifies inoperable disease.

Carotid space

The carotid space is a potential space within the carotid sheath, which is itself formed from a condensation of all three layers of deep cervical fascia. It contains the common carotid artery, the IJV and the vagus nerve.

Parotid space

The parotid space is formed by the investing layer of deep cervical fascia that splits to encompass the parotid gland and therefore contains the facial nerve, the retromandibular vein and the terminal branches of the external carotid artery.

Visceral space

The visceral space is bounded by the middle layer of deep cervical fascia that envelops the thyroid and the trachea anteriorly and posteriorly by the pretracheal fascia. It contains the larynx, hypopharynx, cervical oesophagus, proximal trachea, thyroid and parathyroid glands and lymphatics of level VI.

KEY POINTS

- The inter-connected neck spaces act as potential routes for spread of infection and malignancy.
- Collections within the submandibular space and deep neck spaces readily result in airway obstruction if untreated and can make endotracheal intubation problematic due to distorted and displaced anatomy.
- Parapharyngeal space infection may occur directly or because of spread from the submandibular or peritonsillar spaces.
- The two parapharyngeal spaces communicate with the retropharyngeal space, from where infection can spread into the mediastinum or into the thorax to the level of the diaphragm via the danger space.

MUSCLES

Knowledge of the muscles of the neck is key to understanding neck anatomy, acting as important landmarks in the neck and forming the boundaries of the triangles of the neck. The muscles of the neck may be divided into groups: the superficial muscles, suprahyoid and infrahyoid muscles and the prevertebral muscles.

Superficial neck muscles

PLATYSMA

The platysma is a thin sheet of muscle that encases the neck. It is covered by superficial cervical fascia and is attached inferiorly to the deep fascia of pectoralis major muscle of the anterior chest wall. Superiorly it attaches to the inferior border of the mandible and is often deficient in the midline, however some fibres cross the midline and interweave below the mentum. Inferiorly it is continuous with the fascia of the pectoralis major muscle. The thinness of the platysma means that it has little functional significance; however, it does play a role in depressing the angle of the mouth as some superior fibres blend with the risorius muscle. The muscle derives its blood supply from a plexus of vessels within the muscle, which also supply the skin, as mentioned previously. The arterial supply is from branches of the facial artery superiorly and the suprascapular artery inferiorly, the venous drainage is via the facial vein and internal and external jugular veins. The innervation is from the cervical branch of the facial nerve which runs deep to the muscle (**Table 35.5**).

STERNOCLEIDOMASTOID

The sternocleidomastoid muscle is the most prominent muscle in the neck and is an important landmark as it divides the neck into anterior and posterior triangles along its posterior border. The muscle is encased by the investing layer of deep cervical fascia and lymph nodal levels II to IV are located deep to the muscle. The upper part of the muscle overlies the cervical plexus and the lower half overlies the carotid sheath and the scalenus anterior.

Inferiorly the sternocleidomastoid has both sternal and clavicular origins as two separate heads. The sternal head arises as a thick tendon, attached to the anterior and lateral surface of the manubrium. The clavicular head is fan shaped, arising from the medial third of the clavicle. Superiorly it inserts into the lateral aspect of the mastoid tip and the superior nuchal line. Although classified as a single muscle the two heads are functionally distinct with most of the sternal head attaching to the superior nuchal line and the clavicular head mainly to the mastoid tip. The action is complex; causing tilting of the head to the ipsilateral side and rotation of the head to the contralateral side. When both sides contract simultaneously it aids in head flexion and can assist in raising the thorax when the head is fixed, acting as an accessory muscle of respiration.

The blood supply to the muscle is in three segments. The superior third is supplied from the occipital artery and the posterior auricular artery. The middle third receives blood from a branch from the superior thyroid artery and the inferior third supply is from the suprascapular artery. Perforators from the sternocleidomastoid supply the skin inferiorly which is the basis for the sternocleidomastoid flap. The spinal accessory nerve, which normally passes through the muscle, provides motor function, with sensation and proprioception supplied by the ventral rami of C2–4.

TRAPEZIUS

The trapezius is a key landmark in head and neck surgery as it defines the posterior limit of the posterior triangle. All lymphatic zones and important anatomical structures lie anterior to the trapezius, with only prevertebral muscles and nerves posterior to the muscle. The trapezius is a broad, diamond-shaped sheet of muscle, arising in the midline from the skull to the lower thorax. The superior origin is from the superior nuchal line and the ligamentum nuchae to the level of the seventh cervical vertebra and inferiorly it arises from the spinous processes and interspinal ligaments down to the twelfth thoracic vertebra. Superiorly it has fibres that insert into the clavicle, with inferior fibres inserting into the spine of the scapula.

The trapezius is the main anti-gravity muscle of the shoulder, providing postural stability, and relieves some of the compression load of the head on the cervical spine. The active movements include tilting and turning the head and shrugging the shoulders. The trapezius elevates, depresses and rotates the scapula.[18] The arterial blood supply is via the transverse cervical artery. The accessory nerve provides motor supply to the trapezius muscle with contributions from the cervical plexus derived from C3 and C4 nerve roots. The cervical plexus branches mainly provide proprioception, however studies have proven a contribution to the motor function of the transverse and ascending parts of the

TABLE 35.5 Superficial neck muscles

Muscle	Origin	Insertion	Innervation	Blood supply
Platysma	Inferior border of mandible	Continuous with fascia of pectoralis major muscle	Cervical branches of facial nerve	Plexus with supply from facial artery superiorly, suprascapular artery inferiorly
Sternocleidomastoid	Manubrium, medial 1/3 clavicle	Mastoid tip, superior nuchal line	Spinal accessory nerve, C2–4	Occipital, post auricular, superior thyroid and suprascapular arteries
Trapezius	Superior nuchal line, ligamentum nuchae down to C7 Spinous processes	Clavicle and spine of scapula	Spinal accessory nerve, cervical plexus from C3, C4	Transverse cervical artery

muscle from the cervical plexus branches. Disruption of the motor supply to the trapezius causes shoulder droop and a winged scapula with difficulty in elevating the ipsilateral arm above the head and weakness when shrugging the shoulder. Chronic neck pain is often a feature of trapezius paralysis.

Suprahyoid muscles

The four suprahyoid muscles lie superiorly to the hyoid bone in the neck and act upon the hyoid, elevating it during swallowing, amongst other functions. This group includes the digastric, stylohyoid, mylohyoid and geniohyoid muscles (**Table 35.6**). Whilst not a suprahyoid muscle, rather an extrinsic tongue muscle, we have also included the hyoglossus muscle as it can be a helpful landmark for structures that pass between the mylohyoid and hyoglossus.

DIGASTRIC

The digastric muscle is named as such because it has two bellies, joined in the middle by an intermediate tendon that passes through a sling attached to the lesser cornu of the hyoid bone. The posterior belly arises from the digastric notch on the medial aspect of the mastoid tip. The anterior belly inserts into the digastric fossa of the medial surface of the mandible near the midline. The anterior belly lies superficially to the mylohyoid muscle. The anterior bellies from each side define the submental triangle and the anterior and posterior bellies define the submandibular triangle as described above. The origin of the posterior belly at the digastric ridge is a landmark for the depth of the facial nerve as it exits the stylomastoid foramen.

The arterial blood supply is from branches of the facial artery anteriorly and the occipital artery posteriorly. The nerve supply to digastric reflects its embryological origins from the first and second branchial arch; the posterior belly is supplied by a branch of the facial nerve, the nerve to digastric and the anterior belly is supplied by the nerve to mylohyoid, from the maxillary division of the trigeminal nerve. The digastric muscle depresses the chin to assist in mouth opening and elevates the hyoid during swallowing.

STYLOHYOID

The stylohyoid muscle is related to the posterior belly of digastric, which it runs alongside. Its function is to elevate the hyoid bone during swallowing. It arises from the styloid process of the mastoid tip and it inserts into the lesser cornu of the hyoid bone. A tendon is formed in the mid portion of the muscle that splits around the sling that the digastric tendon passes through. The innervation of the stylohyoid is from the nerve to digastric from the facial nerve and the blood supply is from branches of the facial and occipital arteries.

MYLOHYOID

The mylohyoid muscle forms the floor of the mouth, its function is to support the weight of the tongue and elevate the hyoid bone during deglutition. It arises from the mylohyoid line, on the inner surface of the mandible and inserts into the anterior surface of the body of the hyoid bone. The two muscles meet at the midline, forming a midline raphe from the hyoid to the mentum. The submandibular salivary gland wraps around the free posterior border of the mylohyoid muscle. The mylohyoid is a muscle of the first pharyngeal arch and is innervated by the inferior alveolar nerve, from the mandibular division of the trigeminal nerve. The arterial blood supply is from the branches of the facial artery.

GENIOHYOID

The geniohyoid muscle arises from the genial tubercle on the inner surface of the mandible at the midline and runs deep to mylohyoid to insert into the upper part of the body of the hyoid bone. Like mylohyoid, the geniohyoid provides support to the floor of mouth and elevates the hyoid, but also acts to depress the mandible during mouth opening. The innervation is from C1 nerve roots that run with the hypoglossal nerve and the blood supply is from branches of the facial artery.

HYOGLOSSUS

The hyoglossus lies posterior and deep to the mylohyoid muscle, with fibres originating from the body and greater

TABLE 35.6 Suprahyoid muscles

Muscle	Origin	Insertion	Innervation	Blood supply
Digastric	Digastric ridge, mastoid tip	Digastric fossa, inner surface mandible	Anterior belly: Trigeminal neve Posterior belly: Facial nerve	Anterior belly: Facial artery Posterior belly: Occipital artery
Stylohyoid	Styloid process	Lesser cornu hyoid	Nerve to digastric from facial nerve	Facial artery Occipital artery
Mylohyoid	Mylohyoid line of mandible	Anterior surface of body of hyoid	Inferior alveolar nerve from trigeminal	Facial artery
Geniohyoid	Genial tubercle	Body of hyoid	C1 nerve roots with hypoglossal nerve	Facial artery
Hyoglossus	Body and greater cornu of hyoid	Inserts into tongue	Hypoglossal nerve	Lingual artery

TABLE 35.7 Infrahyoid muscles

Muscle	Origin	Insertion	Innervation	Blood supply
Sternohyoid	Medial clavicle and manubrium	Lower body of hyoid	C1, C2, C3	Superior thyroid artery
Sternothyroid	Posterior surface of manubrium	Oblique line of thyroid cartilage	C1, C2, C3	Superior thyroid artery
Omohyoid	Lower body of hyoid	Scapula	C1, C2, C3	Inferior thyroid artery
Thyrohyoid	Greater horn of hyoid	Oblique line of thyroid cartilage	C1, C2, C3	Superior thyroid artery

cornu of the hyoid before entering the tongue. The lingual vein passes medially and the lingual artery passes deep to hyoglossus. Several important structures run between the mylohyoid and the hyoglossus muscles; the sublingual gland, submandibular duct, lingual nerve, and the hypoglossal nerve. The innervation is from the hypoglossal nerve and it derives its arterial blood supply from the lingual artery.

Infrahyoid muscles

The infrahyoid muscles, commonly termed the 'strap' muscles, lie inferior to the hyoid bone. This group consists of the sternothyroid, sternohyoid, thyrohyoid and omohyoid muscles which have the common action of depressing the hyoid and larynx to modify resonance during voice production. They oppose the elevators of the hyoid, stabilizing the hyoid during action of the mylohyoid and the digastric. They are all innervated by the ansa cervicalis with fibres from C1, C2 and C3.

STERNOHYOID

The sternohyoid is the most superficial of the strap muscles and the largest. It arises from the medial clavicle, the sternoclavicular joint and the upper manubrium and inserts into the lower body of the hyoid bone. The two muscles are joined in the midline at a midline raphe, a relatively bloodless plane that must be dissected to unlock the central compartment for thyroidectomy and tracheostomy procedures.

STERNOTHYROID

Deep to the sternohyoid is the sternothyroid muscle, arising from the posterior surface of the manubrium and first costal cartilage and inserting into the oblique line of the thyroid cartilage. Deep to the sternothyroid lies the thyroid gland, both the sternohyoid and sternothyroid must be retracted to enable access to the thyroid lobes.

OMOHYOID

The omohyoid muscles has two bellies, joined by a flat tendon at the point where the muscle passes over the IJV. The superior belly arises from the lower body of the hyoid bone and runs inferiorly, just lateral to the sternohyoid muscle and deep to sternocleidomastoid and across the IJV. The inferior belly then travels an oblique course to insert into the scapula posteriorly.

THYROHYOID

The thyrohyoid is the smallest of the infrahyoid muscles and attaches the thyroid cartilage to the hyoid bone.

Prevertebral muscles

Contained within the prevertebral fascia are the prevertebral muscles, a group of weak neck flexors. This muscular group can be subdivided into anterior and lateral groups.

ANTERIOR PREVERTEBRAL MUSCLES

The anterior prevertebral muscles lie deep to the prevertebral fascia and anterior to the spinal column and include the rectus capitus anterior, rectus capitus lateralis, longus capitus, longus colli and splenius capitus. Their combined action is to flex and bow the head.

LATERAL PREVERTEBRAL MUSCLES (SCALENE MUSCLES)

The lateral prevertebral muscles, also known as the scalene muscles, are of more significance in head and neck surgery than the anterior group, due to the many important relations of the anterior scalene muscle. The phrenic nerve runs on the superficial surface of the anterior scalene muscle and the second part of the subclavian artery passes posterior to the scalenus anterior, where it gives off the costo-cervical trunk. The transverse cervical, ascending cervical and suprascapular arteries lie superficial to the muscle. The roots of the brachial plexus arise between the scalenus anterior and scalenus medius and emerge on the lateral border of scalenus anterior. The branches of the brachial plexus carry with them a layer of prevertebral fascia, which also encases the subclavian artery and becomes the axillary sheath.

KEY POINTS

- The superficial neck muscles provide important anatomical boundaries and are covered by layers of cervical fascia.
- The supra-hyoid and infra-hyoid muscles act antagonistically to elevate, depress or stabilize the hyoid for speech and swallowing.
- The anterior scalene muscle and its relationships to the phrenic nerve, brachial plexus and subclavian artery provide vital anatomical knowledge relating to the root of the neck and Chassaignac's triangle.

CERVICAL LYMPHATICS

The lymphatics of the neck are divided into superficial and deep systems. The superficial lymphatics drain the skin and perforate the investing layer of deep cervical fascia to drain into the deep system. When affected by malignancy, these lymph nodes will quickly invade the skin necessitating skin resection to ensure complete excision.

The deep lymphatics are associated with fascial condensations and are in proximity to the vessels, nerves and muscles of the neck. Over 80% of lymph nodes in the neck are closely related to the IJV. The deep lymphatic system is divided into nodal groups as depicted in **Figure 35.9**, or classified into nodal levels, demonstrated by **Figures 35.10** and **35.11**.

Lymphatic flow is typically in a downwards direction and may pass through many nodal zones. In the event of metastatic lymphadenopathy from an unknown primary the nodal zone involved can help to predict the primary site due to the somewhat predictable pattern of lymphatic spread, in the previously untreated patient. In the context of previous neck dissection, the pattern of regional lymphatic involvement is much less predictable and may readily involve any remaining lymphatic areas of the ipsilateral neck, the retropharyngeal lymph nodes and the contralateral neck.

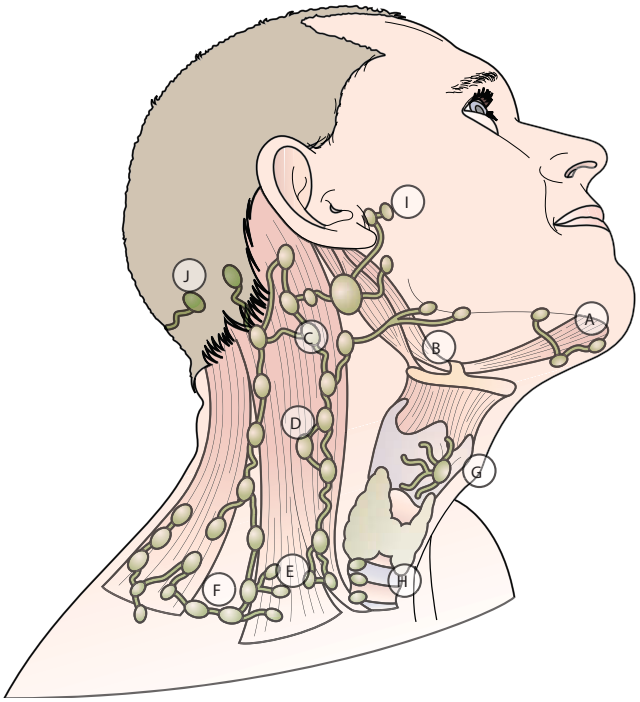


Figure 35.9 Lymph node groups.

Lymph node levels

The classification of lymph node zones into levels originates from the Memorial Sloan Kettering Hospital, New York and was adopted by the American Academy of Otolaryngology Head and Neck Surgery (AAOHNS) in 1991.[19] This clinically orientated classification system was developed by surgeons and radiologists and aims to differentiate nodal areas that drain the visceral structures of the head and neck.

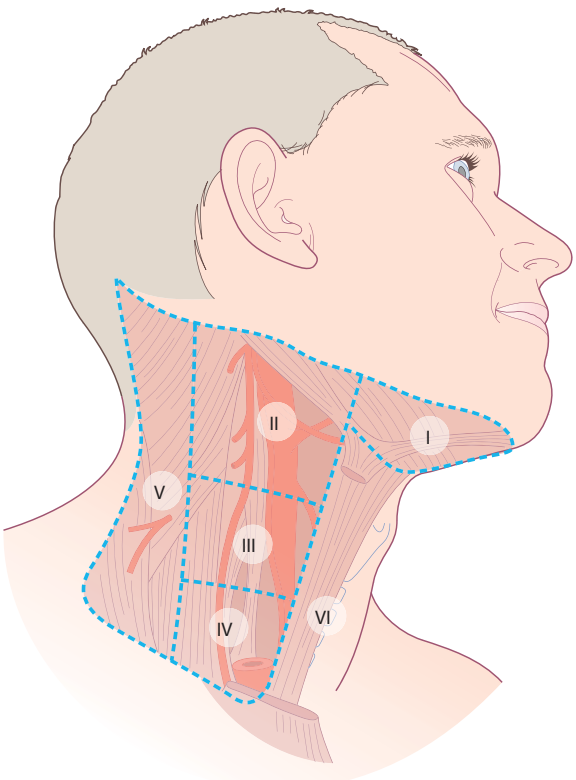


Figure 35.10 Lymph node levels.

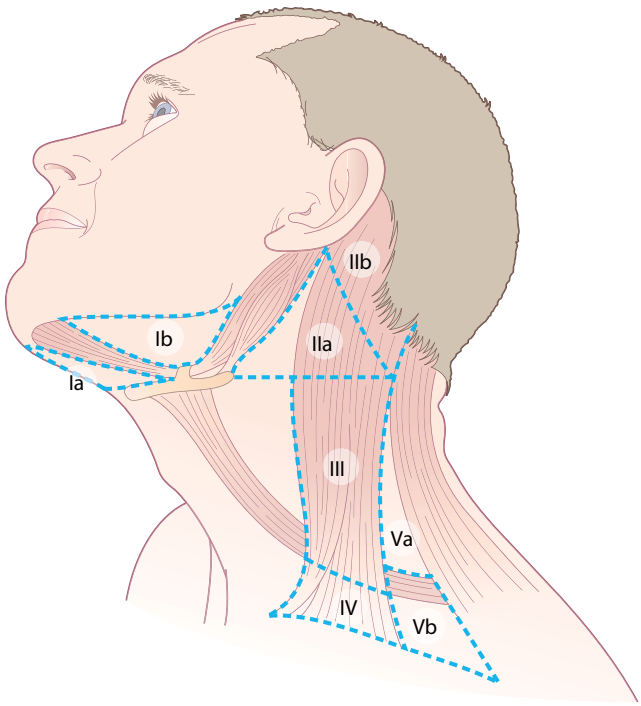


Figure 35.11 Lymph node zones and subzones.

LEVEL IA

This nodal area is a single midline zone, corresponding to the submental triangle, between the two anterior bellies of digastric and the hyoid bone. The submental lymph nodes are located within this level, which provides lymphatic drainage to the anterior floor of mouth, lower lip and ventral tongue.

LEVEL IB

This level is located within the submandibular triangle and contains the submandibular lymph nodes. Drainage from lateral oral cavity structures such as the lateral tongue, floor of mouth and buccal cavity is to these lymph nodes, which are closely related to the facial vessels.

LEVEL II

The lymphatics of level II are the uppermost nodes of the jugular chain, extending from the skull base to the level of the inferior border of the hyoid bone. Level II lymphatics are the first echelon lymph nodes of the oropharynx, but also drain the oral cavity, nasopharynx, hypopharynx and larynx, as well as the parotid gland. Lymphatic drainage from the submandibular and retropharyngeal nodes joins the jugular system at the junctional nodal area, at the lower aspect of level II. The spinal accessory nerve subdivides level II into IIa and IIb as described below.

LEVEL IIA

Caudal to the spinal accessory nerve is level IIa. The presence of nodal disease in IIa mandates dissection of IIb during neck dissection.

LEVEL IIB

Cranial to the spinal accessory nerve is level IIb, also known as Suárez's triangle, named after the Argentinian who first described functional neck dissection in the 1960s. This nodal level covers a triangular area with the apex at the junction of the posterior border of the sternocleidomastoid muscle and the posterior belly of digastric and is bounded inferiorly by the accessory nerve. The occipital artery may be encountered in the superior aspect of this nodal zone.

LEVEL III

Level III refers to the lymph nodes of middle jugular chain, from the level of the inferior border of the hyoid to the inferior aspect of the cricoid cartilage. This zone receives lymphatic drainage from the lower areas of the oropharynx, the hypopharynx and larynx.

LEVEL IV

This zone extends from the level of the inferior border of the cricoid to the clavicle and contains the lymph nodes of the lower jugular chain, which drain the hypopharynx and larynx. The omohyoid muscle crosses the superior aspect of this level. Low in level IV, within Chaissaignac's triangle in the root of the neck, lymph node metastasis may occur from an infraclavicular primary source, typically bronchus or breast. Furthermore, Virchow's node, a supraclavicular lymph node metastasis from upper gastrointestinal malignancy, is located in level IV on the left side of the neck.

LEVEL V

Level V represents the posterior triangle lymph nodes. This zone covers a large area, with a thin layer of fibrofatty tissue over the prevertebral musculature, extending from a superior apex formed by the junction of the trapezius and sternocleidomastoid muscles to the clavicle inferiorly. The anterior limit is the posterior border of the sternocleidomastoid muscle and the posterior limit is the anterior border of trapezius. The spinal accessory nerve runs across the roof of level V and the transverse cervical artery is found in the inferolateral aspect of this zone. The lymphatics of level V receive drainage from all other nodal areas but are also a common location for metastatic involvement from nasopharyngeal or cutaneous scalp primary lesions. Level V is subdivided into Va and Vb by an imaginary horizontal line at the level of the inferior border of the cricoid cartilage.

LEVEL Va

This subzone is the area above the boundary line and contains the lymph nodes related to the spinal accessory nerve, which runs in the roof of level Va. Much of nodal tissue is located caudal to the nerve.

LEVEL Vb

This represents the nodal area below the level of the inferior border of the cricoid cartilage and contains the level V lymph nodes related to the transverse cervical artery and the supraclavicular lymph nodes.

LEVEL VI

This single midline zone, also termed the anterior or central compartment, is located between the common carotid arteries laterally. The superior border is the inferior aspect of the hyoid. The inferior boundary is defined as the innominate artery on the right side of the neck and the corresponding level on the left side.[20] The paratracheal, perithyroid and precricoid (Delphian) nodes are in this zone. Nodal metastasis in this area may arise from primaries in the thyroid, the glottis or subglottic larynx, the apex of the piriform fossa or the cervical oesophagus. Lymph node dissection of the central compartment is commonly performed in conjunction with total thyroidectomy for malignancy or total laryngectomy and may result in postoperative hypocalcaemia because of inadvertent removal of the parathyroid glands which are also located within this nodal zone.

LEVEL VII

This refers to the lymph nodes of the superior mediastinum which may be accessed via the neck, or via an access sternotomy. These lymph nodes may harbour metastasis from thyroid, subglottic or tracheal or cervical oesophageal malignancies. The thymic remnant is also found in this area.

KEY POINTS

- The patterns of lymphatic drainage within the neck are site specific.
- The flow of lymph is from superficial to deep and then from cephalic to caudal direction.
- There are approximately 100 lymph nodes on either side of the neck which range in size from 3 mm to 3 cm with a mean of 1 cm.
- The cervical lymph nodes are divided into levels the dissection of which forms the basis of selective neck dissection.
- Selective neck dissection is based upon site specific drainage and is therefore best suited to the untreated neck.
- Incisions in the neck can alter lymphatic drainage for up to one year after surgery.
- Previous treatment of the neck, in the form of surgery and or radiotherapy, alters lymphatic drainage which can result in unpredictable patterns of metastatic lymphadenopathy, including involvement of the parapharyngeal and retropharyngeal spaces.

NERVES

Knowledge of the anatomy of the nerves of the neck is essential when operating in the neck to avoid unnecessary morbidity from major nerve injury. The important nerves of the neck are the lower cranial nerves, the spinal nerves of the cervical plexus, the cervical sympathetic trunk and the brachial plexus.

Cranial nerves

FACIAL NERVE

The facial nerve is the nerve of the second branchial arch. Its main function is to supply motor innervation to the muscles of facial expression, with smaller branches that also provide motor supply to the posterior belly of digastric and the stylohyoid muscle. After leaving the cranium through the internal auditory meatus and passing through the middle ear space and mastoid, the main trunk of the facial nerve exits the temporal bone via the stylomastoid foramen. It then traverses the parotid gland where it divides into five main branches within the gland. Known as the 'pes anserinus', literally meaning the 'goose's foot', these branches are the temporal, zygomatic, buccal, marginal mandibular and cervical branches; the latter two are the branches found in the neck.

MARGINAL MANDIBULAR NERVE

The marginal mandibular branch of the facial nerve is the main branch of the lower division of the facial nerve. It takes a variable course and may have up to four branches in the neck. The nerve passes antero-medially across the upper neck in the plane just deep to the platysma muscle but superficial to the investing layer of deep cervical fascia. It can extend as low as the greater cornu of the hyoid bone, before passing superficial to the facial vessels and across the mandible to provide motor supply to the depressor anguli oris, depressor labii inferioris and mentalis muscles. Its action is to move the corner of the mouth and lower lip, however the nerve supply to the lower lip is multifactorial, with contributions from the cervical branch of the facial nerve and the platysma muscle, meaning that if any one of these mechanisms is interrupted lower facial asymmetry may occur.

This nerve is most at risk during submandibular gland excision and clearance of lymph node level I for malignant disease. The nerve can be protected by incising the investing layer of deep cervical fascia inferior to the lower border of the submandibular gland or just above the hyoid bone and reflecting the fascia superiorly along with the facial vein, retracting the nerve out of the surgical field.

CERVICAL BRANCH OF THE FACIAL NERVE

The lowest branch of the facial nerve, the cervical branch supplies the platysma muscle. It can be identified travelling antero-inferiorly and may give off multiple branches. Injury to this branch can cause asymmetry of the corner of the mouth due to the contribution of the platysma to the movement of the lower lip.

GLOSSOPHARYNGEAL NERVE

The glossopharyngeal nerve is the ninth cranial nerve and the nerve of the third branchial arch. It exits the skull via the anterior compartment of the jugular foramen, then passes between the IJV and the ICA, before descending anterior to the ICA. It then curves anteriorly around the stylopharyngeus muscle, deep to hyoglossus and either pierces the lower fibres of the superior constrictor or runs between superior and middle constrictor muscles. Fibres are then distributed to the palatine tonsil, mucosa of the pharynx and posterior tongue and minor salivary glands of the oral mucosa and the oropharynx. The glossopharyngeal nerve is historically described as 'the nerve of economy' due to the way it is considered to spread itself thinly between the structures it supplies; providing motor supply to one muscle, special sensory supply to one area, visceral sensation to one organ, parasympathetic fibres to one secretory gland and general sensation to other areas.

The glossopharyngeal nerve has many branches, some of which communicate with other nerves. It sends filaments that communicate with the sympathetic trunk, the vagus and facial nerves. The clinically relevant branches are:

- **The tympanic nerve:** Also known as Jacobson's nerve, this branch supplies the tympanic plexus and is the reason for referred otalgia secondary to pain affecting the oropharynx.
- **The lesser petrosal nerve:** This branch provides postganglionic secretomotor supply to the parotid gland and passes through the infratemporal fossa.

- **Carotid sinus and carotid body branches:** These branches take afferent nerves from the chemoreceptor in the carotid body and baroreceptors from the carotid sinus.
- **Pharyngeal branches:** These branches join the fibres from the vagus nerve and the sympathetic trunk to form the pharyngeal plexus, which sits on the posterior aspect of the middle constrictor muscle. Small nerves from the plexus perforate the muscle fibres of the middle constrictor muscle and innervate the mucosa of the oropharynx. The pharyngeal branches provide somatic sensation. The tonsillar branch anastomoses with the lesser palatine nerves to supply the mucous membrane of the palatine tonsil. Injury to the pharyngeal plexus may lead to swallowing dysfunction.
- **Motor branch:** The main motor branch of the glossopharyngeal nerve innervates the stylopharyngeus muscle.
- **Lingual branches:** These provide common sensation, taste and secretomotor supply to the posterior third of the tongue.

VAGUS NERVE

The vagus nerve derives its name from the Latin word 'vagi', meaning 'roaming', due to the wandering course that it takes from the cranium to the abdomen. It is the nerve of the fourth branchial arch and is the Xth cranial nerve. The vagus nerve leaves the skull via the middle compartment of the jugular foramen. The superior ganglion of the vagus is located just inferior to the jugular foramen and contains cell bodies for afferent fibres of meningeal and auricular branches. Lower in the neck the nerve dilates to form the inferior ganglion which contains afferent cell bodies of the other branches. The accessory nerve contributes a branch to the vagus nerve which provides motor innervation to all of the visceral striated muscle supplied by the vagus. The vagus nerve runs posteriorly in the carotid sheath, between the IJV and common carotid artery. The vagus gives off the following branches in the neck:

- **Auricular branch:** Also known as Arnold's nerve, this branch passes between the mastoid and the tympanic plate to provide sensory supply to the tympanic membrane and skin of the posterior pinna and posterior ear canal; a further mechanism for referred otalgia.
- **Carotid body branches:** This small branch supplements the branches of the glossopharyngeal nerve that supply the carotid body chemoreceptors.
- **Pharyngeal branch:** The vagal contribution to the pharyngeal plexus derives from the spinal accessory fibres that join the vagus nerve before branching off as the pharyngeal branch. These fibres cross the internal carotid to join the pharyngeal plexus, providing motor innervation to the pharyngeal constrictors and soft palate, in combination with the glossopharyngeal nerve and sympathetic trunk.
- **Superior laryngeal nerve:** The superior laryngeal nerve is given off high in the neck and passes inferior to the ICA, before travelling antero-inferiorly towards the larynx. At the level of the hyoid the nerve branches into the internal and external laryngeal nerve. The internal laryngeal nerve penetrates the thyrohyoid membrane superior to the superior laryngeal artery and provides sensory innervation to the laryngeal and piriform fossa mucosa, with some motor contribution to the interarytenoid muscle and motor and sensory supply to the cervical oesophagus and trachea. The external laryngeal branch is much smaller and runs with the superior thyroid artery on the sidewall of the inferior constrictor before piercing it to provide motor supply to the cricothyroid muscle, the only intrinsic laryngeal muscle not supplied by the recurrent laryngeal nerve. The human communicating nerve is an inconstant branch of the external branch of the superior laryngeal nerve, found as a normal variant in approximately 45% of healthy subjects. It is believed to provide additional motor supply to the thyroarytenoid muscle and sensory supply to the subglottic mucosa. This communicating branch may anastomose with the recurrent laryngeal nerve or may directly supply the thyroarytenoid muscle. This branch was first discovered during early anatomical studies of the larynx but later forgotten as it was not felt to have functional significance, however recent histological studies demonstrate positive staining for acetylcholinesterase, thereby proving motor function of this branch.[21]
- **Cardiac branches:** These branches leave the vagus low in the neck to form the cardiac plexus.
- **Recurrent laryngeal nerve:** The path of the recurrent laryngeal nerves differs on each side of the neck. The reason for this asymmetry is rooted in its embryological development as the nerve of the sixth branchial arch. The artery of the sixth arch is the ductus arteriosus which obliterates on the right whilst it descends into the thorax on the left side, taking the left recurrent laryngeal nerve with it. The left recurrent laryngeal nerve leaves the vagus in the lower part of the neck, before looping around the ligamentum arteriosum and arch of the aorta and then ascending back into the neck in the tracheo-oesophageal groove. The right recurrent laryngeal nerve has a more variable path but usually hooks around the subclavian artery before passing medially towards the tracheo-oesophageal groove. The right nerve takes a non-recurrent course in approximately 1% of individuals. The relationship of the recurrent laryngeal nerve and the inferior thyroid artery is variable but of great significance in thyroid surgery as the nerve may run deep to the artery, superficial to it or between its branches, before it perforates the cricothyroid membrane. The recurrent laryngeal nerve provides motor innervation to all the intrinsic laryngeal muscles except cricothyroid and provides sensory supply to the mucosa of the larynx inferior to the vocal folds. A helpful landmark for identifying the recurrent laryngeal nerve is Beahr's triangle (**Figure 35.12**), which is formed by the common carotid artery laterally, the inferior thyroid vessels and the recurrent laryngeal nerve.

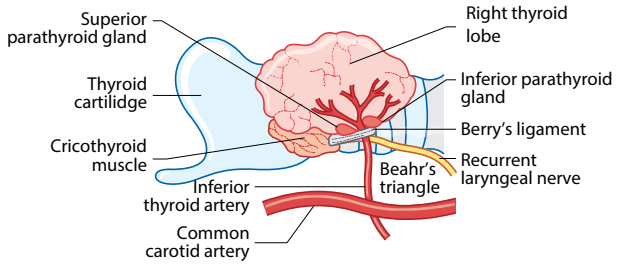


Figure 35.12 Beahr's triangle.

SPINAL ACCESSORY NERVE

The spinal accessory nerve is so called because of the accessory fibres that it contributes to the vagus nerve. This motor nerve constitutes both spinal and cranial origins; fibres from the anterior horn cells in the upper five or six segments of the cervical spinal cord pass intracranially through the foramen magnum to join fibres from the cranial root. The combined fibres then exit the skull via the middle compartment of the jugular foramen, and then pass deep to the styloid process and the posterior belly of the digastric muscle. The nerve then courses across level II, before penetrating the sternocleidomastoid muscle which it supplies, with sensory contribution from the cervical plexus.

The course of the accessory nerve after leaving the sternocleidomastoid varies. It usually leaves the posterior aspect of the muscle one centimetre above Erb's point, where the cervical plexus branches emerge, however the point of emergence is variable and the nerve may not pass through the muscle at all. From the sternocleidomastoid the nerve runs in the roof of the posterior triangle to the trapezius, deep to the investing fascia and superficial to the prevertebral fascia within the fibro-fatty tissue. All-important structures of the posterior triangle are located caudal to the nerve. The nerve reaches the trapezius at the junction of the lower and middle one-third of the anterior surface of the muscle and enters the deep surface of the muscle.

The spinal accessory nerve is thought in most subjects to be the sole motor innervation for the sternocleidomastoid. The trapezius is solely innervated by the spinal accessory nerve in approximately one-quarter of individuals, meaning that in the majority the trapezius also receives a degree of motor innervation from the cervical plexus.[22] In some individuals, the motor branch to trapezius arises from the spinal accessory high in the neck before the accessory nerve enters the sternocleidomastoid muscle so care should be taken in this area to preserve all potential branches. Proprioceptive fibres from the anterior roots of the spinal cord supply the sternocleidomastoid and the trapezius muscles as part of the cervical plexus and may also carry motor fibres. The proprioceptive innervation of sternocleidomastoid is mostly from C2 and C3 and the supply to trapezius is mostly C3 and C4.

The commonest cause of iatrogenic accessory nerve damage is during level V neck dissection, which may be permanent or transient. This leads to denervation of all or part of the trapezius muscle, resulting in difficulty elevating the arm, winging of the scapula and reduced support for the weight of the arm which can lead to intractable cervical nerve root pain.

HYPOGLOSSAL NERVE

The hypoglossal nerve is solely a motor nerve and provides motor innervation to all the intrinsic muscles of the tongue and all extrinsic muscles except palatoglossus, which is supplied by the vagus nerve. After exiting the skull via the hypoglossal canal, the nerve runs deep to the IJV and courses around the vagal ganglion. It then curves around the carotid bifurcation as it heads anteriorly, passing inferior to the greater horn of the hyoid before coursing superiorly, superficial to hyoglossus to reach the tongue. The hypoglossal nerve is susceptible to injury during surgical procedures in the neck, particularly at its lowest point near the hyoid so care must be taken in these areas, to avoid the devastating effect of a hypoglossal nerve palsy on speech and swallowing.

C1 nerve root fibres run with the hypoglossal nerve, giving off a branch known as the descendens hypoglossi that arises at the level of the carotid bifurcation. This branch courses inferiorly, running on the anterior surface of the IJV and joins with cervical plexus branches to form the ansa cervicalis, providing motor supply to the strap muscles.

CERVICAL PLEXUS NERVES

The cervical plexus nerves arise from the anterior rami of the upper four cervical spinal nerves. The cervical plexus lies deep to the prevertebral fascia and passes over the scalenus medius muscle. It has motor and sensory branches (**Figure 35.13**).

The sensory, or cutaneous branches of the cervical plexus emerge from the posterior border of the sternocleidomastoid muscle 1 cm superior to the emergence of the spinal accessory nerve at a point termed Erb's point. These branches provide sensory innervation to the anterior neck, with four named branches:

- **Lesser occipital nerve:** Formed entirely from the C2 root this branch provides supply to the skin posterior to the pinna, up to the superior nuchal line.
- **Greater auricular nerve:** This branch is formed from C2 and C3 nerve roots and runs superiorly from Erb's point, across the sternocleidomastoid muscle towards the parotid gland. It branches into anterior and posterior divisions. The anterior branch supplies sensation to the skin anterior and inferior to the pinna whereas the posterior branch supplies the inferior pinna including the lobule, the skin inferior to the pinna and provides innervation to the parotid capsule. The nerve is often injured during neck dissection or parotid surgery and may have to be sacrificed to enable access to these areas, resulting in insensate lobule and numbness of the upper neck and peri-auricular skin.

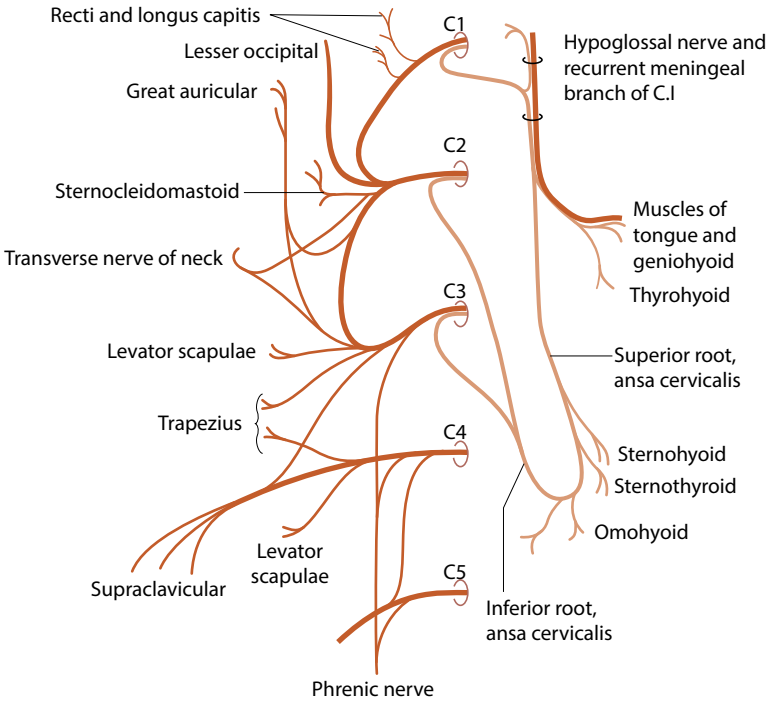


Figure 35.13 Cervical plexus nerves.

- **Transverse cervical nerves:** Fibres from the C2 and C3 nerve roots combine into a single nerve that leaves Erb's point then passes anteriorly and branches multiple times to give sensory innervation the skin of the entire anterior neck.
- **Supraclavicular nerves:** C3 and C4 nerve root fibres combine to form a single nerve which branches after Erb's point into three main divisions. A medial branch supplies an area of skin down to the sternoclavicular joint, the intermediate branch supplies the anterior chest wall skin, down to the anterior axial line. The lateral branch supplies the skin over the deltoid muscle and as far posterior as the spine of the scapula.

The muscular branches are given off segmentally to the prevertebral muscles of longus capitis, longus colli and the scalene muscles. The other muscular branches are the superior and inferior roots of the ansa cervicalis, segmental branches to the sternocleidomastoid and trapezius muscles and the phrenic nerve.

- **Ansa cervicalis:** Named as such from the Latin word 'ansa' meaning 'loop' this nerve is formed from a superior root, the C1 fibres of the descendens hypoglossi and an inferior root from the ventral rami of C2 and C3. The two roots merge over the IJV to form the ansa cervicalis which supplies motor innervation to the infrahyoid muscles: the sternothyroid, sternohyoid, thyrohyoid and omohyoid muscles.
- **Segmental supply to sternocleidomastoid and trapezius muscles:** As previously discussed, whilst the spinal accessory nerve provides the main motor supply to these muscles each also receives motor contribution from the cervical plexus. Branches from C2 and C3 supply the sternocleidomastoid whilst C3 and C4 fibres supply the trapezius. This is evidenced by the preservation of some of the motor supply to these muscles after sacrifice of the spinal accessory nerve during neck dissection. Conversely, shoulder dysfunction may still commonly occur when the accessory nerve is preserved, as a result of injury to the cervical plexus branches that contribute motor innervation to trapezius.
- **Phrenic nerve:** The phrenic nerve is the most significant motor branch of the cervical plexus. Formed from the ventral rami of C3, C4 and C5 the phrenic nerve runs inferiorly on the anterior surface of the scalenus anterior, deep to the prevertebral fascia to provide the sole motor supply to the diaphragm. The phrenic nerve is identifiable as the only structure deep to the prevertebral fascia that runs from lateral to medial. In addition to providing motor supply to the diaphragm it also provides sensory innervation to the central tendon of the diaphragm This is the cause of referred pain to the shoulder tip secondary to diaphragmatic irritation from abdominal or chest pathology that is referred via the C4 root of the phrenic nerve which communicates with the C4 root of the supraclavicular nerve.

CERVICAL SYMPATHETIC TRUNK

The cervical sympathetic trunk runs on the anterior surface of the prevertebral fascia, deep to the carotid sheath. It may have between two and four ganglia but typically has three, the superior, middle and inferior ganglia.

- **Superior cervical ganglion:** This is the largest of the ganglia and provides sympathetic innervation to the skin of the face and neck, including the eyes and eyelids.
- **Middle cervical ganglion:** This ganglion provides parasympathetic supply to the thyroid and parathyroid

glands and has a cardiac branch which supplies the heart, oesophagus and trachea.
- **Inferior cervical ganglion:** Also known as the stellate ganglion when fused with the highest thoracic ganglion, this receives contributions from C7, C8 and T1 and supplies the upper limb, lower neck and the heart.

Injury to the cervical sympathetic trunk may occur during head and neck surgery causing Horner syndrome, characterized by ipsilateral ptosis and meiosis with anhydrosis of the facial skin due to disruption of the oculosympathetic pathway. Horner syndrome is a rare complication of thyroid surgery due to an anatomical variation whereby a communicating branch between the recurrent laryngeal nerve and the cervical sympathetic trunk exists, which is at risk during thyroidectomy.

BRACHIAL PLEXUS

The brachial plexus is formed from the ventral rami of C5 to C8 and T1 and provides motor and sensory supply to the upper limb. It emerges between the anterior and middle scalene muscles and courses posteriorly across the inferior aspect of the posterior triangle, deep to the prevertebral fascia. It is an important structure for head and neck surgeons to appreciate as injury can have a catastrophic effect on the patient. It is most at risk during neck dissection, particularly when operating low in the posterior triangle or if the prevertebral fascia is breached.

KEY POINTS

- Knowledge of the anatomy of cranial and cervical nerves in the neck is key to operating safely in the neck.
- Care must be taken to avoid injury to the accessory nerve in the posterior triangle; all important structures lie caudal to the nerve.
- Supplementary motor supply from the cervical plexus to the sternocleidomastoid and trapezius muscles should be preserved where possible to optimize function.
- During neck dissection, with the fascial layers under tension, the sensory nerves of the cervical plexus travel medially and upwards, allowing sharp dissection away from the important motor nerves of the cervical and brachial plexus.
- There are rare connections between the recurrent laryngeal nerve and cervical sympathetic trunk which, if divided, can result in ptosis following thyroidectomy.

BLOOD VESSELS

The common carotid artery, branching in the neck into the internal and external arteries, provides the main arterial blood supply to the neck, with venous drainage via the jugular venous system.

Common carotid artery

The common carotid artery arises from the arch of the aorta on the left and from the brachiocephalic artery, also termed the innominate artery, on the right side. It does not normally give off branches, however, the vertebral, superior thyroid, inferior thyroid, ascending pharyngeal or occipital arteries may arise directly from the common carotid as normal variants.

The common carotid artery travels in the carotid sheath with the IJV and the vagus nerve. The cervical sympathetic trunk lies deep to the carotid sheath. The common carotid artery branches into internal and external branches at the level of the greater cornu of the hyoid bone. At the point of the bifurcation the artery dilates to form the carotid sinus, which contains stretch receptors innervated by the glossopharyngeal nerve which are the body's main baroreceptors. The carotid body lies deep to the bifurcation and contains chemoreceptors innervated by the glossopharyngeal nerve.

External carotid artery

The external carotid artery gives off multiple branches after the bifurcation which supply the viscera and muscles of the neck and face. The external carotid gives off six branches before dividing into two terminal branches within the parotid gland (**Table 35.8**). Although the superior thyroid artery is the first branch to be encountered, the ascending pharyngeal branch may arise first but is located deep to the main trunk and may not be readily visible. When ligating the external carotid artery for epistaxis, the ascending pharyngeal branch was traditionally preserved, because of its supply to the skull base and dura.

Internal carotid artery

The internal carotid artery (ICA) has no branches in the neck and lies deep and lateral to the external branch after the bifurcation. It runs beneath the posterior belly of digastric to enter the skull via the carotid canal and provides blood supply to the intracranial contents, with the vertebral artery via the circle of Willis. Important relations of the ICA are the IJV which runs antero-laterally to the artery and the pharynx, superior laryngeal nerve and pharyngeal vessels which are situated medial to the artery.

TABLE 35.8 Branches of the external carotid artery

Branch	Location	Supplies
Ascending pharyngeal	Deep	Oropharynx, hypopharynx, skull base, dura
Superior thyroid	Anterior	Thyroid, sternocleidomastoid
Lingual	Anterior	Tongue
Facial	Anterior	Tongue, tonsil, superficial facial soft tissue
Occipital	Posterior	Sternocleidomastoid, occiput
Posterior auricular	Posterior	Pinna, post-auricular skin
Superficial temporal	Terminal	Temporal region, scalp
Maxillary	Terminal	Deep facial tissues, mandible, nasal cavity

The cervical sympathetic trunk and its superior ganglion lie deep to the internal carotid.

Subclavian artery

The right subclavian artery arises from the brachiocephalic artery, whereas the left arises from the arch of the aorta, in a similar arrangement to the common carotid arteries. The subclavian arteries travel laterally towards the arm. The first part of the subclavian artery, from its origin to the medial aspect of the anterior scalene muscle, gives off the vertebral artery, the internal thoracic artery and the thyrocervical trunk, from which the inferior thyroid artery, suprascapular artery and the transverse cervical artery arise. The first part of the subclavian artery lies deep to sternocleidomastoid and the strap muscles but may extend above the clavicle so is at risk during procedures in the supraclavicular fossa. The second part of the artery runs deep to the anterior scalene muscle and gives off the costocervical trunk and the dorsal scapular artery. The third part passes lateral from the edge of the anterior scalene towards the arm and has no branches in the neck.

Internal jugular vein

The lateral or sigmoid dural venous sinus continues into the neck as the internal jugular vein (IJV). The jugular bulb lies within the floor of the tympanic cavity. After exiting the skull via the jugular foramen, the IJV travels inferiorly in the carotid sheath, anterior and lateral to the carotids. The IJV receives tributaries from the inferior petrosal vein, the common facial vein, the pharyngeal venous system and the superior and middle thyroid veins. Important relations of the jugular vein include the carotid arteries as mentioned above and the vagus nerve which runs posteriorly in the carotid sheath. The sternocleidomastoid muscle lies superficial to both the IJV and the carotid arteries, providing protection from penetrating trauma. The posterior belly of digastric and the inferior belly of the omohyoid muscle both cross over the IJV.

Inferiorly the IJV drains into the brachiocephalic veins on both sides, with only one valve before draining into the superior vena cava and eventually into the right atrium. Because of backflow from the right atrium the IJV has a pressure wave. The thoracic lymphatic duct drains into the posterior aspect of the IJV, at the intersection with the subclavian vein in Chassaignac's triangle.

Facial veins

The venous drainage of the face and oral cavity is via the facial and lingual veins which then form a venous plexus in the submandibular triangle. These may drain into the jugular vein with one single tributary that drains into the common facial vein or there may be many tributaries. The common facial vein also receives some drainage from the retromandibular vein which passes through the parotid gland.

Superficial jugular veins

Both the anterior jugular vein and the external jugular vein are part of a variable superficial venous system that drains the face and scalp. They drain into the subclavian vein, where valves exist to prevent backflow; thus the superficial jugular veins have low pressure, unlike the IJV.

KEY POINTS

- It is important to remember the ICA has no branches in the neck and lies deep and lateral to the external carotid.
- Both the internal and external carotid arteries are intimately related to the glossopharyngeal nerve and the pharyngeal and laryngeal branches of the vagus nerve, as well as the vagus nerve itself, the hypoglossal nerve and the cervical sympathetic trunk.
- Access to lymphatic level II is facilitated by retraction of the digastric; when doing so it is important to remember that vital vascular structures lie immediately deep to the muscle.
- When dissecting the hypoglossal nerve difficult bleeding can be encountered from the venae comitantes nervi hypoglossi and from a network of veins draining the thyroid, face and tongue known as the thyroglossofacial confluence which empty into the IJV in this location.
- Division of the common facial vein facilitates access to the hypoglossal nerve.
- When ligating any important vascular structure in the neck given a name, transfixion of the vessel should be considered to avoid haemorrhage.
- During thyroidectomy there are only two structures encountered within the para-carotid tunnel. These are the non-recurrent nerve and the middle thyroid vein; care should be taken when dividing this close to the IJV.

SUMMARY

Preservation of function when operating in the neck is more important than ever in this era of conservation surgery and improved survivorship from head and neck cancer. Functional neck surgery is not possible without a sound understanding of neck anatomy. This chapter covers the clinically relevant surgical anatomy of the neck to highlight the key areas any surgeon operating in the neck should be aware of. Advances in head and neck imaging aids surgeons in planning operations by providing detailed anatomical imaging, however, a sound knowledge of head and neck anatomy from texts and most importantly from clinical experience of operating in the neck remains key to providing patients with the highest standards of surgical care.

ACKNOWLEDGEMENTS

The authors would like to acknowledge the contribution that Mr Owain Rhys Hughes made to this chapter.

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CHAPTER 36

CLINICAL EXAMINATION OF THE NECK

James O'Hara

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SEARCH STRATEGY

Data in this chapter may be updated by a search of PubMed using the keywords: clinical examination AND neck OR salivary glands, Head and Neck neoplasms AND Lymphatic metastases OR Neck metastases.

INTRODUCTION

Clinical examination of the neck should accompany a thorough history and appropriate ear, nose and throat assessment. It is performed in either acute or elective settings, during assessment of a primary upper aerodigestive symptom, primary neck lump complaint or surveillance following treatment.

INSPECTION

The patient should ideally be exposed from the clavicles. Observe for lumps, skin changes and scars. Ask the patient to point to any lump if one is not obvious. Patients with midline lumps should be observed whilst drinking a sip of fluid and protruding the tongue. The thyroid gland is enveloped in pre-tracheal fascia along with the trachea. It will rise with laryngeal elevation during swallowing. Ask the patient to hold the fluid in the mouth before swallowing, giving the examiner time to concentrate on any movement. A thyroglossal cyst will elevate with tongue protrusion, being attached via the thyroglossal duct remnant to the foramen caecum of the tongue. Ask the patient to open their mouth, observe the lump and then ask them to protrude the tongue. Pemberton's sign is elicited by asking the patient to sit and raise the arms.[1] Venous congestion with facial plethora or cyanosis may indicate thoracic outlet obstruction for which a retrosternal goitre is a cause. Examination of the oral cavity to assess the parotid and submandibular ducts should accompany a thorough neck examination.

Examine the relevant cranial nerve function. Metastatic lymphadenopathy in the region of the accessory nerve can cause reduced function. It is important to note this prior to any proposed surgery. Parapharyngeal tumours may cause impairment to the nerves from which they arise, for example, Glomus vagale or Schwannoma of the sympathetic chain, or can cause compression to other lower cranial nerves.

Examine the scalp and external ear closely for lesions where appropriate. Skin conditions often cause level V reactive lymph nodes. Cutaneous squamous cell carcinoma and melanoma, often previously excised, may metastasize to the parotid lymph nodes and cervical nodes.

In the acute presentation, observe the patient for how the neck is held and for neck movements. Acute torticollis in a septic patient, usually a child, is indicative of severe inflammation and pain. Reduced range of neck movement in a septic patient may indicate a deep neck space abscess.

PALPATION

Have a set method that is reproducible. The location of the noted pathology in the neck should lead the examiner to consider a list of differential diagnoses (**Table 36.1**).

TABLE 36.1 Basic differential diagnosis of neck lumps

Lymph node group	Differential diagnosis
IA (submental)	Lymph node Thyroglossal cyst Dermoid cyst Plunging ranula
IB (submandibular)	Submandibular gland pathology Lymph node Cystic hygroma / lymphangioma (both can affect the entire neck)
II (upper jugular)	Lymph node Parotid gland pathology Branchial cyst Parapharyngeal pathology (e.g. Paragangliomata or nerve sheath tumours)
III (mid jugular)	Lymph node Branchial cyst Parapharyngeal pathology Laryngocoele
IV (lower jugular)	Lymph node (including Virchow's node on the left)
V (posterior triangle)	Lymph node Lipoma Cervical rib
VI (anterior compartment)	Thyroid gland pathology Thyroglossal cyst Parathyroid neoplasm Lymph node Direct extension of a laryngeal neoplasm

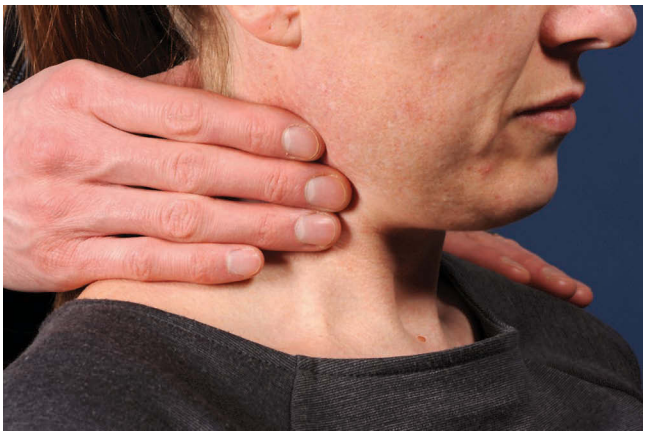

Figure 36.1 Palpation of the neck.

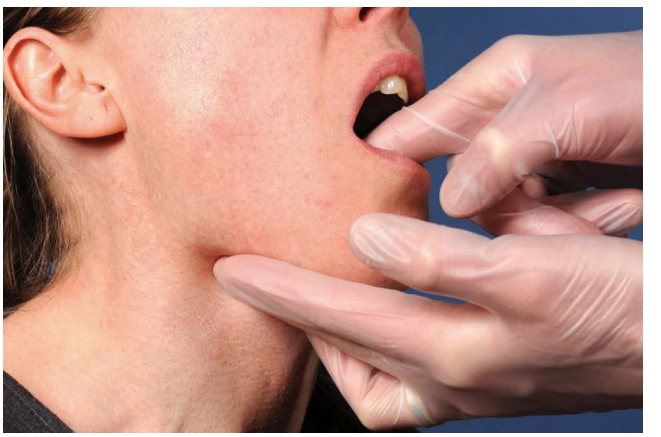

Figure 36.2 Bimanual palpation of the salivary glands.

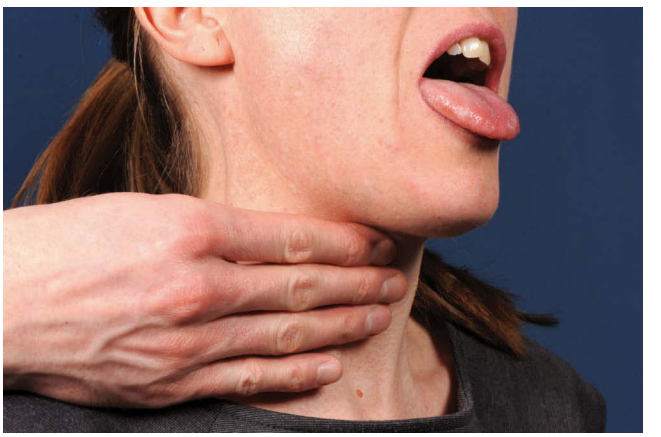

Figure 36.3 Palpation of a suspected thyroglossal cyst.

Each side of the neck should be examined individually, not simultaneously as this may cause excessive vagal stimulation through carotid sinus massage. The neck should be slightly flexed with the head tilted to the side of examination. This relaxes the neck muscles, in particular the sternocleidomastoid, allowing palpation of structures deep to it. The flats of the fingers should be used to palpate in a slow sweeping manner and should not resemble piano playing (**Figure 36.1**). The author always starts at level IA, sweeping posteriorly into IB before examining the jugular chain lymph nodes from level II to IV. The fingers then pass from medial to lateral above the clavicle before sweeping superiorly, anterior to the trapezius, towards the mastoid tip, covering level V. The post-auricular region, occipital and parotid regions are then palpated. Bimanual palpation of the salivary glands should be performed for any salivary lump (**Figure 36.2**). A suspected thyroglossal cyst is palpated in the same manner as during inspection (**Figure 36.3**). Finally the thyroid gland is palpated. This organ can be examined with both hands and the swallowing assessment repeated if necessary. Thyroid nodules may be palpable in 4–7% of the population, rising with age.[2] When detected as a part of an examination for other symptoms, thyroid nodules are not classified as 'incidentalomas' (as they are when detected with imaging) since they are by definition palpable. These nodules require investigation with serum thyroid-stimulating hormone (TSH), thyroid ultrasound with fine-needle aspiration where appropriate. Bear in mind normal anatomical structures which may seem pathological; the transverse process of the C2 vertebra, a prominent carotid bifurcation or occasionally patients may be aware of a normal internal jugular vein on voluntary valsalva.

PERCUSSION

Percussion over the sternum may give an indication of the extent of a retrosternal goitre or other upper mediastinal mass.

AUSCULTATION

Auscultation of the carotid arterial flow is often advocated for patients with symptoms suggestive of cerebral insufficiency. A study of 2000 patients found that 'critical auscultation' had a sensitivity of 83% and specificity of 40% in detecting carotid bifurcation lesions.[3] It concluded that auscultation is not capable of excluding carotid lesions. Auscultation over the larynx and trachea may help further characterize stridor, especially helpful in children.

CLINICAL EVALUATION OF CERVICAL LYMPHADENOPATHY

The majority of clinical neck examinations are performed to assess the cervical lymph nodes. The site, size, number, consistency, fixity to surrounding structures and overlying skin appearances should be assessed. For lymph nodes considered to contain metastatic head and neck malignancy, the affected site or sites should be classified according to the level(s) of the neck. The concept of 'levels' of the neck was first proposed by Shah in 1990.[4] Subsequently the Committee for Neck Dissection Classification of the American Head and Neck Society published several consensus documents further defining these levels.[5,6] The most recent anatomical boundaries of the neck levels are summarized in **Table 36.2** (**Figure 36.4**). Physical examination alone has a sensitivity of 81% and specificity of 77% in detecting metastatic lymphadenopathy.[7]

TABLE 36.2 Classification of neck levels

Lymph node group	Anatomical boundaries
IA (submental)	Laterally the anterior belly of digastric muscles, inferiorly the hyoid bone, superiorly the mandible.
IB (submandibular)	Anteriorly the anterior belly of digastric muscle, superiorly the body of the mandible, posteriorly the vertical plane defined by the posterior border of the submandibular gland (updated in 2008). This level includes the submandibular gland.
II (upper jugular – divided into A and B)	Medially the vertical plane defined by the posterior border of the submandibular gland (updated in 2008), laterally the posterior border of the sternocleidomastoid muscle, superiorly the skull base and inferiorly the inferior border of the hyoid bone. The vertical plane defined by the accessory nerve divides level II into A, anterior and medial and B, posterior and lateral.
III (mid jugular)	Medially the medial aspect of the common carotid artery (2008), laterally the posterior border of the sternocleidomastoid muscle, superiorly the inferior border of the hyoid bone, inferiorly the inferior border of the cricoid cartilage.
IV (lower jugular)	Medially the medial aspect of the common carotid artery, laterally the posterior border of the sternocleidomastoid muscle, superiorly the inferior border of the cricoid cartilage, inferiorly the clavicle.
V (posterior triangle – divided into A and B)	Medially (anterior) the posterior border of sternocleidomastoid muscle, posteriorly the anterior border of the trapezius muscle, superiorly the convergence of the sternocleidomastoid and trapezius, inferiorly the clavicle. It is divided by the horizontal plane from the inferior border of the cricoid arch into levels VA, superior and containing the nodes around the accessory nerve and VB, inferior containing the nodes around the transverse cervical vessels. Level VB incorporates the supraclavicular nodes, except Virchow's node in level IV.
VI (anterior compartment)	Laterally the medial aspect of the common carotid arteries, superiorly the hyoid bone and inferiorly the suprasternal notch.

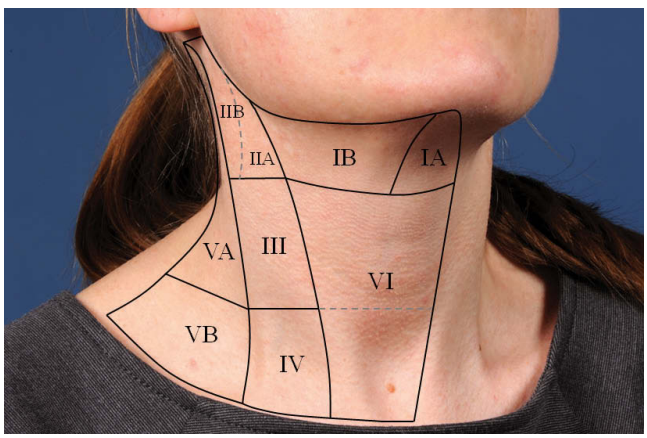

Figure 36.4 Anatomic boundaries of the neck levels.

KEY POINTS

- All patients presenting with head and neck symptoms should undergo a thorough clinical examination of the neck.
- The site of any neck pathology should lead the examiner to consider the potential differential diagnoses.
- Lymphadenopathy secondary to head and neck malignancy should be described according to the involved levels of the neck.

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CHAPTER
37

IMAGING OF THE NECK

Ivan Zammit-Maempel

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SEARCH STRATEGY

Data in this chapter may be updated by a Medline search using the keywords: head and neck cancer, head and neck infections, neck masses, imaging, CT, MRI, ultrasound, PET-CT.

IMAGING TECHNIQUES

Various imaging techniques are used in the evaluation of patients presenting with a neck mass or a 'hot' neck and in the staging and post-treatment follow-up of head and neck cancer. These include plain X-rays, ultrasound, CT, MRI, and PET-CT. Radiologists are increasingly being involved in image-guided biopsies, aspirations of collections in the neck, botox injections in selected post-surgical patients to improve speech or reduce salivary flow and embolizing/stenting vessels in patients with uncontrollable bleeding. Contrast studies including videofluoroscopy and angiography have an important role in selected cases.

The ENT surgeon is often unsure as to which investigation to request and this chapter will aim to clarify this based on the currently available evidence in the literature. However, there is no escaping from a meticulous history and examination in reaching a clinical diagnosis and imaging should be used to confirm this diagnosis and not used as a blanket screening examination.

Imaging modalities have been discussed in more detail in the relevant organ-specific chapters but some brief observations are provided below.

PLAIN X-RAYS

The use of plain X-rays in the head and neck is limited to detecting ingested radio-opaque foreign bodies, assessing the dentition in head and neck cancer patients and those presenting with abscesses around the floor of mouth as well as confirming the presence of air (**Figure 37.1**) or evaluating bony hard masses (**Figure 37.2**).

ULTRASOUND (US)

US is quick, non-invasive, readily available, inexpensive and does not use ionizing radiation but is heavily operator dependent. It is widely used in children for evaluating neck lumps, lymph nodes, the thyroid and salivary glands and in guiding fine-needle aspiration (FNA) or core biopsies. US is particularly helpful in evaluating whether a node appears reactive (**Figure 37.3a**) and can therefore be safely ignored or more complex (**Figure 37.3b**), requiring FNA and further investigation.[1–3]

COMPUTED TOMOGRAPHY (CT)

CT is used extensively in staging head and neck cancer patients and for detecting masses or abscesses in the deep

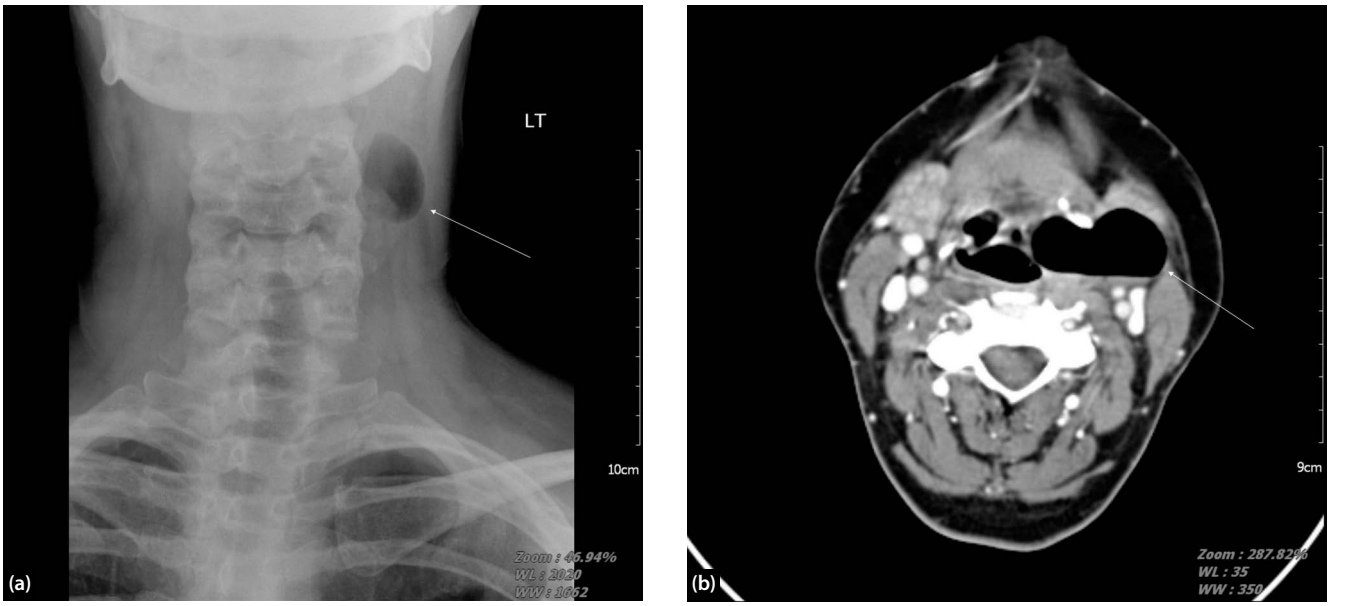


Figure 37.1 Plain X-ray (a) and axial contrast enhanced CT **(b)** showing a left-sided laryngocoele (arrow) in a patient initially referred with a soft swelling for ultrasound.

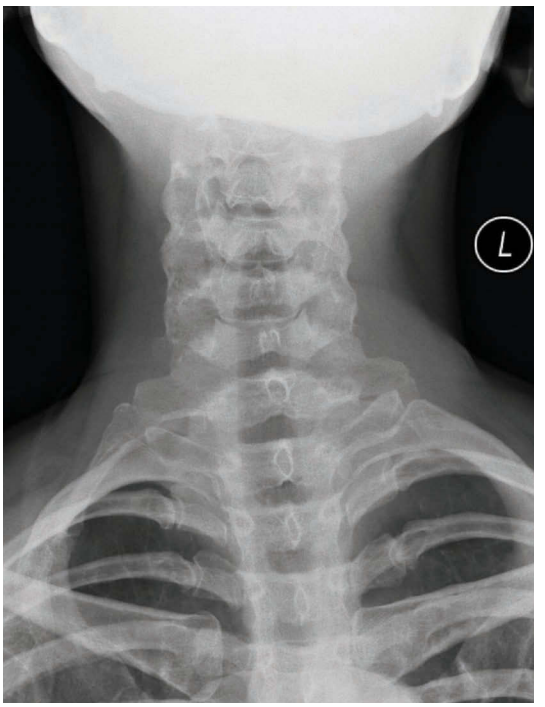


Figure 37.2 Bilateral cervical ribs, larger on the right: patient presented with a bony hard mass in the right supraclavicular region.

spaces of the neck. With the advent of multi-detector scanners, the entire neck can be scanned in a few seconds and a volumetric data set obtained, allowing reconstructions in any plane. Because of its relatively low soft-tissue resolution, intravenous iodinated contrast agents are necessary. Dual-source scanning is the latest breakthrough in CT technology and early results are promising for imaging the neck.[4] Radiation dose is an important consideration on CT and dose reduction can be achieved by special in-built features in most modern CT scanners as well as manually altering settings such as mAs and KV, without affecting diagnostic image quality.[5, 6] Artefact from dental amalgam can be negated by gantry tilt but the combination of this facility and volumetric scanning is not available on all scanners.[7] Cone-beam CT has an evolving role in head and neck imaging.[8]

MAGNETIC RESONANCE IMAGING (MRI)

MRI produces images with very good soft-tissue contrast and does not use ionizing radiation but is contraindicated in certain patients with pacemakers, ferromagnetic intraocular foreign bodies, cochlear implants, cerebral artery aneurysm clips and valve prostheses. The long acquisition times result in neck images that can be easily degraded by movement and swallowing artefact.

POSITRON EMISSION TOMOGRAPHY (PET)

PET is a functional imaging technique that depicts tissue metabolic activity and all hypermetabolic cells, not just malignant cells, accumulate the tracer resulting in increased activity as measured by standard uptake value (SUV). The commonest tracer used is fluorine-18-labelled 2-fluoro-2-deoxy-D-glucose (FDG), which has a half-life of 110 minutes. The combination of CT and PET allows accurate anatomical localization. PET-CT is especially useful in assessing patients presenting with a metastatic neck node and no overt primary, the so-called cancer of unknown primary, and in the post-treatment patient, where differentiation between post-treatment fibrosis and residual/recurrent tumour can be difficult. Head and neck PET-CT is complicated by the fact that various structures such as Waldeyer's ring (lymphoid tissue of the

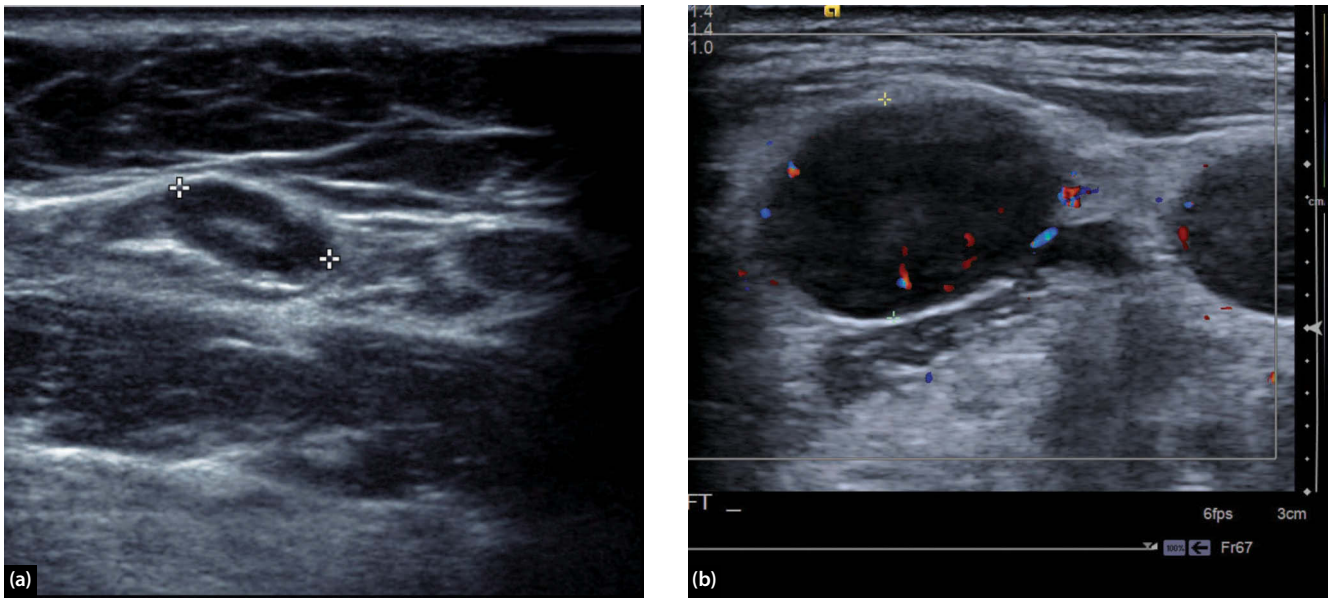


Figure 37.3 US showing a reactive node with a normal echogenic hilum **(a)** and a metastatic node showing loss of its normal architecture and increased peripheral vascularity **(b)**.

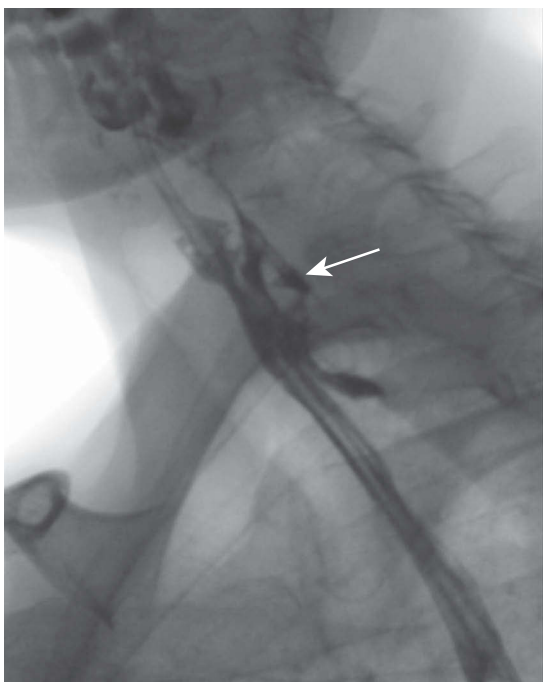


Figure 37.4 Contrast swallow post-laryngectomy showing an inferior leak (arrow) extending into the superior mediastinum.

nasopharynx, tongue base, palatine tonsil, soft palate and posterior pharyngeal wall), the salivary glands, nasal turbinates and cervical muscles normally show FDG uptake. The feasibility of MRI and PET in the staging of head and neck cancer is also being evaluated.[9]

CONTRAST SWALLOW

Contrast swallows are important in assessing for the presence of leaks in the early phase after laryngeal and pharyngeal surgery (**Figure 37.4**) while videofluoroscopy is important in assessing head and neck cancer patients presenting with dysphagia before or after treatment.

HEAD AND NECK CANCER

Imaging plays an important role in assessing the extent of primary tumour and any metastases.[10, 11] Many tumours can initially be staged by CT as the chest and liver can be imaged at the same time as the neck, allowing the detection of distant chest, liver or bone metastases and any synchronous lung or gastrointestinal tumours. MRI is particularly useful for evaluating intracranial spread in nasopharyngeal and other skull-base tumours and the oral cavity in patients where the images are degraded by dental amalgam artefact. Diffusion-weighted MRI is being increasingly used in the head and neck to help with differentiating benign from malignant tumours, squamous cell carcinoma from lymphoma, suppurative lymphadenitis from metastatic nodes, recurrence from post-radiotherapy fibrosis as well as nodal staging.[12–16]

Small mucosal tumours are easily assessed clinically but larger tumours require cross-sectional imaging to assess the size, location and deep extension of tumour, involvement of surrounding structures and presence of distant metastases.

Lymph node status is one of the most important prognostic factors in head and neck cancer and various studies have shown that imaging is more reliable than clinical palpation.[17, 18]

NASOPHARYNGEAL CANCER

The most common cancer of the nasopharynx is undifferentiated or poorly differentiated carcinoma that has a close relationship to the Epstein–Barr virus. Other cancers

that may arise in the nasopharynx include lymphoma, adenocarcinoma, adenoid cystic carcinoma, melanoma, plasmacytoma, chordoma and sarcoma. This chapter will concentrate on nasopharyngeal carcinoma that has a high incidence in the Chinese population, even after they have emigrated.

Nasopharyngeal carcinoma

Nasopharyngeal carcinoma (NPC) is different from other head and neck squamous cell tumours in its aggressive local infiltration and propensity for metastatic spread despite apparently early primary lesions. Patients may present with a neck mass, nasal obstruction, blood-stained nasal discharge, headaches, ophthalmoplegia, hearing loss and tinnitus. The aim of imaging is to accurately map the primary tumour and to detect any extension especially to the skull base and deep fascial planes as well as nodal and distant metastases.

CT allows assessment of the primary tumour, neck nodes, chest and liver in one examination but MRI is superior in demonstrating the tumour soft-tissue extent, any intracranial extension and skull-base bone marrow changes.[19–22] Dynamic contrast-enhanced MRI may be useful in characterizing NPC as higher stage tumours show some parameters of increased permeability and perfusion.[23] PET-CT is useful in staging, assessing for recurrence and in evaluating the nasopharynx in patients presenting with neck nodes and no obvious primary.[24–27] Huang et al.[28] showed that intratumoral heterogenicity of FDG uptake across NPC tumours significantly correlated with tumour aggressiveness and predicted patient outcome while various authors have shown a correlation between SUV and outcome.[29–34] Ng et al. suggest a combination of PET-CT and head and neck MRI as the initial staging examinations for NPC patients, with MRI superior in detecting locoregional invasion and retropharyngeal nodes and PET-CT more accurate in determining cervical node metastases.[35] However King et al. showed that the additional use of PET-CT did not upstage or change management when compared to MRI in their cohort of patients.[36] Imaging may allow differentiation of NPC from lymphoma as NPC is often asymmetrical with a propensity to invade widely and deeply into muscle tissue, fat spaces, neural foramina and skull base while lymphoma is more symmetrical, shows homogenous enhancement and has a propensity to involve Waldeyer's ring.[37–39]

An understanding of the pathology of nasopharyngeal cancer is essential in order to correctly interpret imaging at the time of staging and subsequent follow-up.[40] Most nasopharyngeal tumours originate in the fossa of Rosenmuller and tend to spread submucosally with early infiltration of the palatal muscles and obstruction of the Eustachian tube (**Figure 37.5**). The most common spread is laterally with infiltration of the parapharyngeal and masticator spaces with potential involvement of the mandibular nerve and intracranial spread. Anterior spread of tumour into the nasal fossa can result in erosion of the maxillary sinus and infiltration of the pterygopalatine fossa and thence along the maxillary nerve onto the foramen rotundum (**Figure 37.6**). NPC can spread superiorly to erode the clivus (**Figure 36.7**), petrous apex, sphenoid sinus and foramen lacerum. Inferiorly it can extend along the pharyngeal wall to the oropharynx while posteriorly it infiltrates the retropharyngeal space and prevertebral muscles. Nodal metastases (**Figure 37.8**) to all cervical levels including the retropharyngeal group are extremely common and may be the presenting feature but level 2B nodes rather than retropharyngeal nodes appear to be the first echelon nodes in NPC.[41, 42] Tomita et al. showed that primary tumour existence beyond the midline of the nasopharynx was associated with a higher incidence of bilateral lymph node metastases than primary tumour presence within the midline, with incidences of 66% and 18% respectively.[43] Distant metastases to the lung and liver are common.

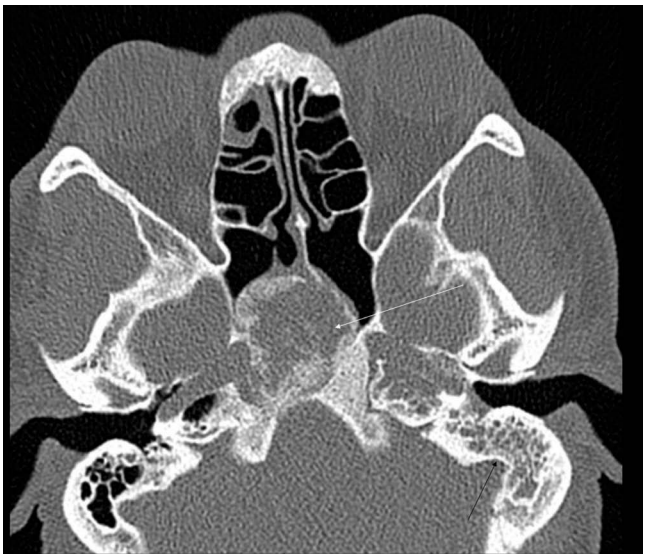


Figure 37.5 Axial CT on bone settings showing nasopharyngeal carcinoma (white arrow) and retained secretions left mastoid air cells (black arrow) due to Eustachian tube obstruction.

Management of NPC is one of the greatest clinical challenges, with radiotherapy, especially intensity-modulated radiotherapy (IMRT), being the primary treatment and chemoradiotherapy used for locoregionally advanced tumours.[44] The aim of post-treatment imaging is to detect early recurrence. As there is usually tumour resolution by 3 months post-radiotherapy, PET-CT is being increasingly used to ensure no residual activity within the primary site or nodes.[26, 45] Differentiating fibrosis from tumour recurrence is difficult on CT and can also be problematic by MRI but 3T-MRI may be comparable to PET-CT in detecting residual or recurrent NPC and contrast-enhanced MRI is useful in detecting perineural spread (**Figure 37.8**).[46–50] The combined use of MRI and FDG PET-CT is more accurate for tumour restaging than either modality used independently.[51] Some authors have suggested plasma Epstein–Barr virus DNA screening and if positive followed by PET-CT while others have advocated the use of CT perfusion in detecting recurrences.[52–54] A systematic review comparing PET-CT, CT

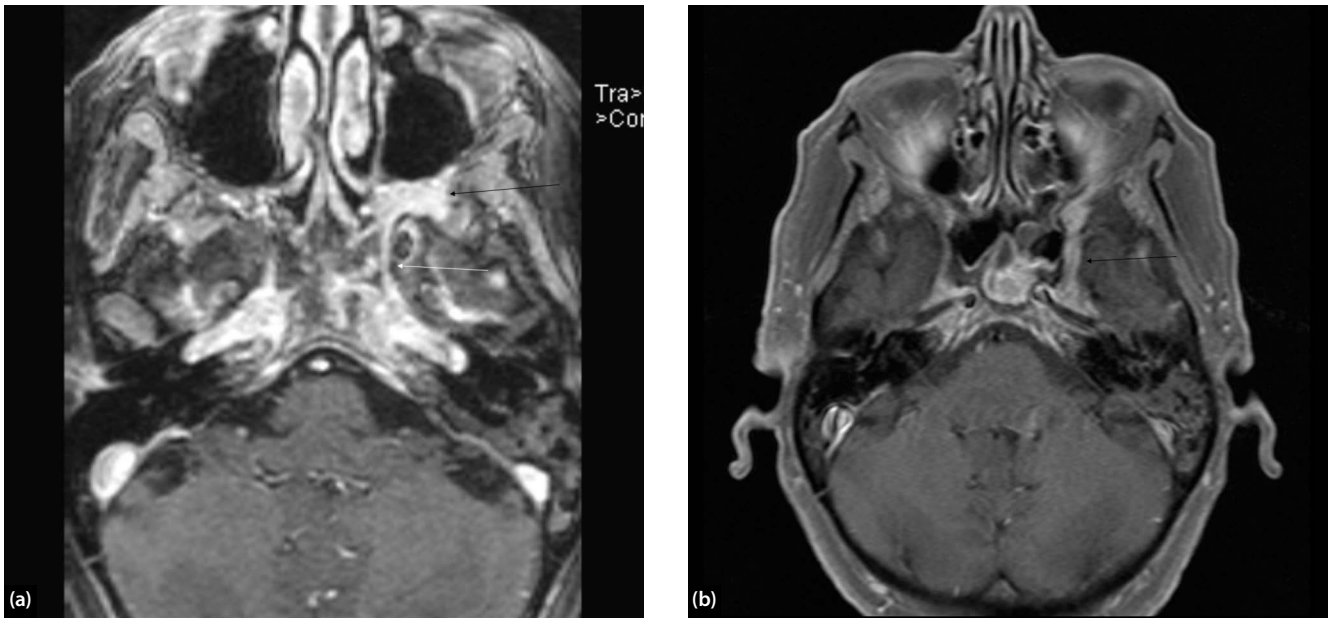


Figure 37.6 Axial VIBE (Volumetric interpolated brain examination) MRI showing left nasopharyngeal cancer (NCC) extending into the pterygopalatine fossa (black arrow) and vidian canal (white arrow) **(a)** and into the foramen rotundum (black arrow) **(b)**.

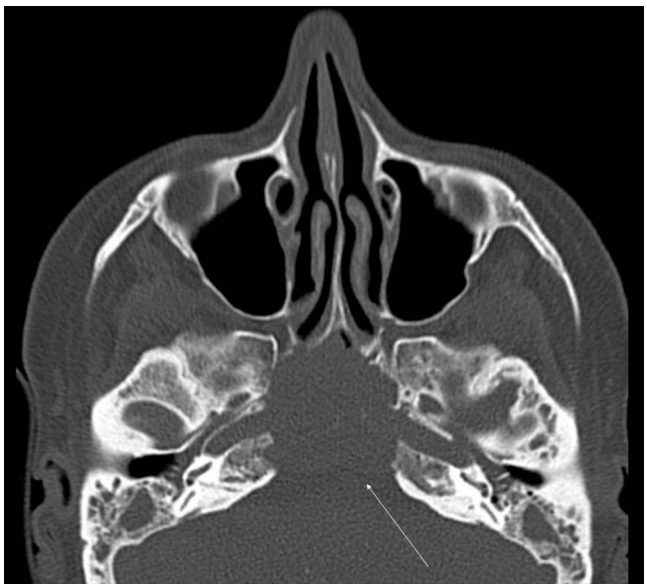


Figure 37.7 Axial CT showing destroyed clivus (white arrow) secondary to NPC.

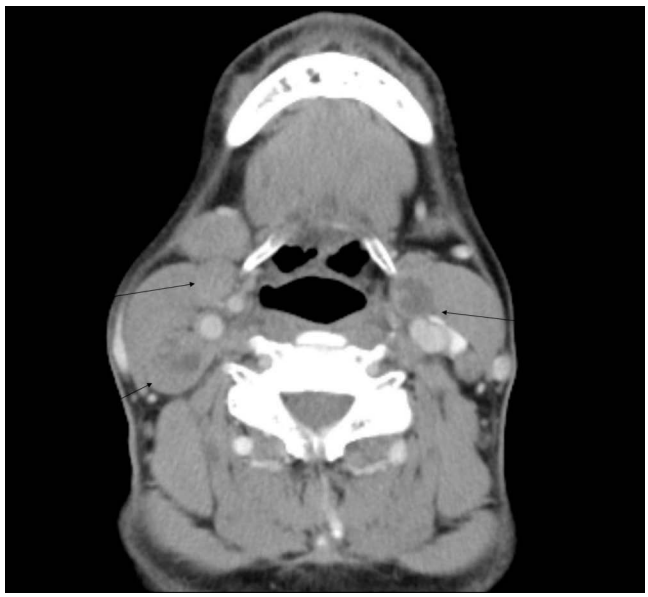


Figure 37.8 Axial contrast-enhanced CT showing bilateral level 2/3 nodes (black arrows) in patient with NPC.

and MR imaging for the diagnosis of local residual or recurrent NPC showed that PET-CT was the best imaging modality.[55] PET-CT should therefore be the imaging modality of choice in the detection of residual or recurrent disease (**Figure 37.9**).

Lymphoma

Non-Hodgkin lymphoma (NHL) is the second most common nasopharyngeal tumour and classically involves Waldeyer's ring.[37–39] Imaging usually demonstrates a well-defined, homogenous, non-necrotic mass that is exophytic rather than infiltrative in nature (**Figure 37.10**).

ORAL CAVITY TUMOURS

The oral cavity is bordered by the hard palate and maxillary alveolar ridge superiorly, the mylohyoid muscle and alveolar mandibular ridge inferiorly, the lips anteriorly, the gingivobuccal region laterally and the soft palate, circumvallate papillae and tonsillar pillars posteriorly. Although the soft palate forms part of the oropharynx, the mucosal layer beneath the hard palate lies within the oral cavity. The centre of the oral cavity is filled by the tongue, the anterior two-thirds of which is part of the oral cavity.

Oral cavity tumours are usually readily apparent clinically and easily amenable to biopsy but challenging for

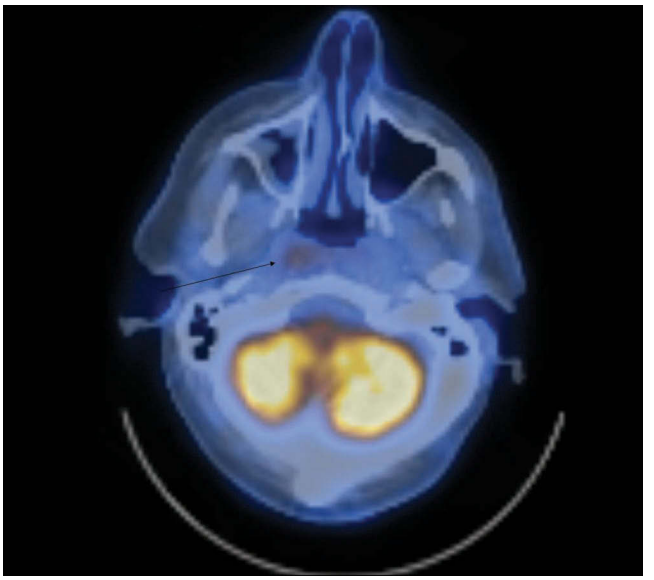


Figure 37.9 Fused axial PET-CT showing activity in the right nasopharyngeal region (black arrow), confirmed histologically to be NPC recurrence.

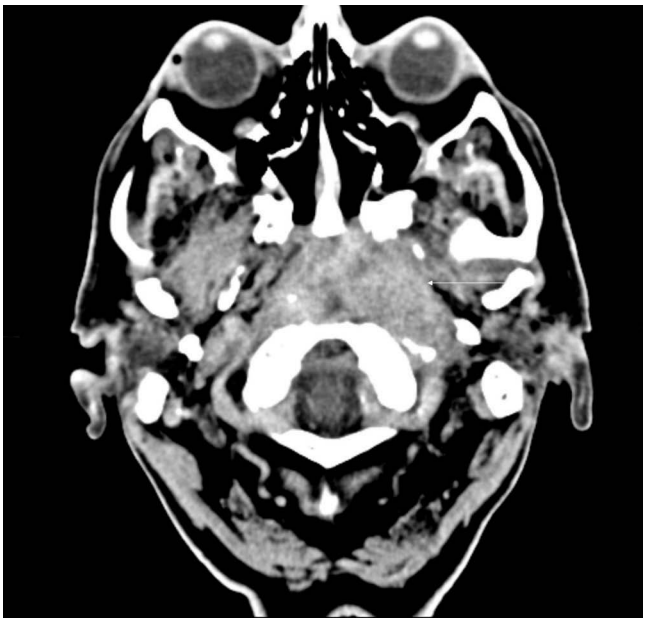


Figure 37.10 Axial CT showing a midline nasopharyngeal mass, biopsy confirmed non-Hodgkin lymphoma.

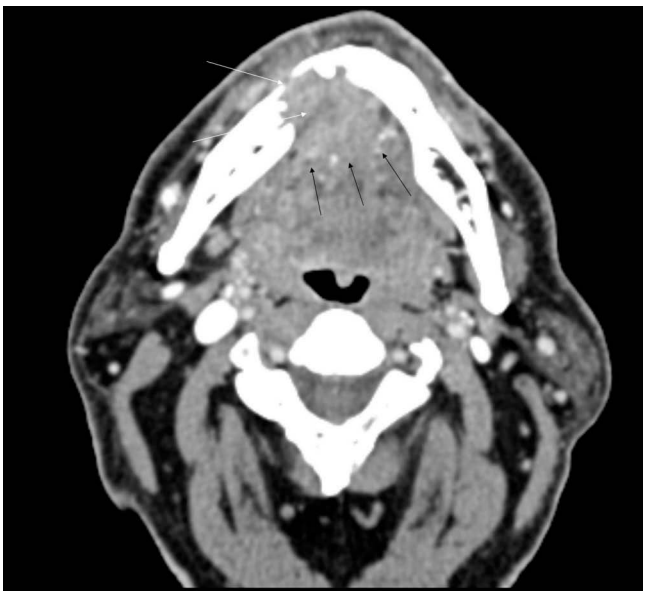


Figure 37.11 Axial contrast-enhanced CT showing anterior floor of mouth SCC crossing the midline (black arrows) with associated destruction of inner and outer cortex of mandible (white arrows).

radiological diagnosis because of the surrounding anatomy and small tumours are often not visualized by imaging. Squamous cell carcinoma (SCC) is the most common tumour that affects the oral cavity and can extend along the submucosa to invade adjacent structures. Despite the invasive character of SCC, bony structures are infiltrated late in the course of disease. The invasion of nerves and vessels is an important aspect in the spread of oral cavity tumours. Vascular invasion results in a greater risk of remote as well as lymph node metastases while perineural extension allows spread far beyond the expected tumour margins. The oral mucosa has bilateral drainage to the level 1 submental and submandibular nodes and any asymmetrically enlarged nodes should be regarded with suspicion. Cervical nodal metastases occur in approximately 50% of patients with SCC of the oral cavity and may be bilateral especially if tumours cross the midline but lymphadenopathy is often occult and not detected clinically or by imaging. The floor of mouth, retromolar trigone (RMT) and ventrolateral tongue are involved in descending frequency by SCC and will be briefly discussed.

Floor of mouth cancer

Most of these tumours are easily diagnosed clinically and occur anteriorly, from where they can extend deeply into the sublingual gland, obstruct the submandibular duct and invade the submandibular space. The key points from the imaging point of view include looking for extension posteriorly along the neurovascular bundle and across the midline (**Figure 37.11**).

Retromolar trigone cancer

The RMT is the triangular mucosa posterior to the last molar and tumours are less easily detected clinically. SCC can arise from the RMT (**Figure 37.12**) or spread into the RMT secondarily from the tongue base or tonsil. Tumours may invade the mandible directly, the inferior alveolar nerve or extend posteriorly along the pterygomandibular raphe, a fibrous band beneath the RMT that extends from the hook of the hamulus of the medial pterygoid to the mylohyoid line on the medial border of the mandibular body. As the buccinator, superior constrictors and orbicularis oris muscles all insert into the pterygomandibular raphe, tumours can extend into the lateral floor of mouth, buccal space, tonsillar fossa or nasopharynx.

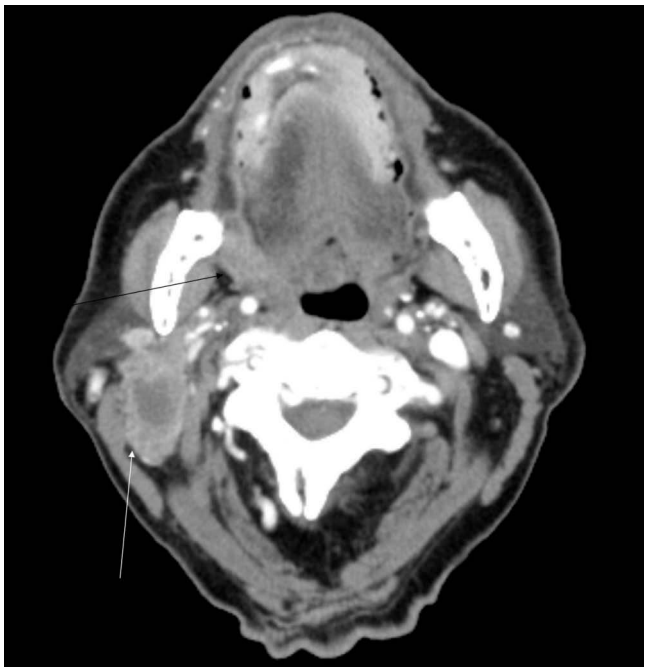


Figure 37.12 Axial contrast-enhanced CT showing a right retromolar trigone tumour (black arrow) with an associated necrotic level 2 node (white arrow).

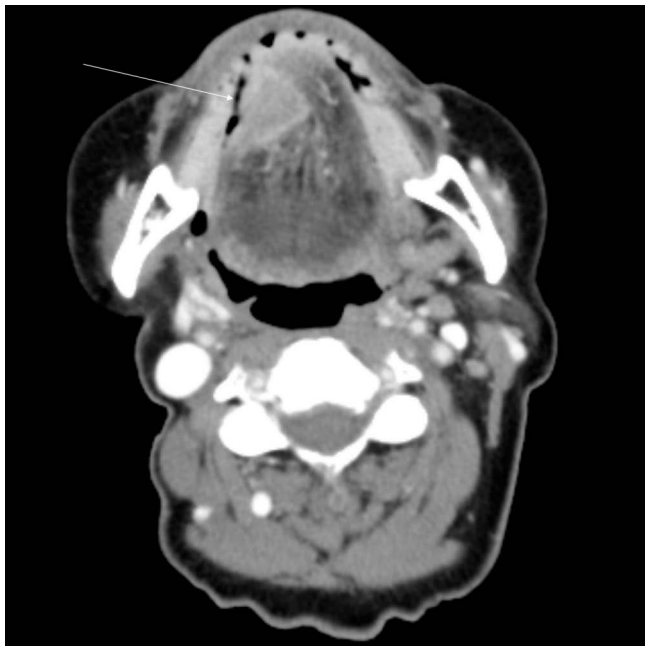


Figure 37.13 Axial contrast-enhanced CT showing right ventral tongue tumour (white arrow) just reaching the midline.

Tongue cancer

The ventrolateral surface of the tongue is the site most commonly involved by tumour (**Figure 37.13**), which can easily invade the intrinsic muscles. Besides assessing for tumour spread into the floor of mouth, tongue base, tonsils, soft palate and mandible, tumour extension across the midline and to the contralateral neurovascular bundle also needs evaluation.

Hard palate, gingival and buccal cancer

The gingiva is the mucous membrane that covers the alveolar bone processes and is attached to the lingual and buccal surfaces of the mandible and maxilla. Gingival and buccal tumours (**Figure 37.14**) may eventually invade the mandibular or maxillary cortex especially in edentulous patients. Hard-palate tumours (**Figure 37.15**) require close evaluation of the bone, best seen in the coronal plane and can spread perineurally along the incisive and greater and lesser palatine canals to the pterygopalatine fossa.

Modalities available for imaging the oral cavity are ultrasound, CT, cone-beam CT, MRI and PET-CT.[56–63] As in other head and neck cancers, CT provides better evaluation of cortical bone while MRI has the advantage of better characterizing local tumour extent, perineural spread and bone-marrow involvement. Dental amalgam artefact poses a frequent diagnostic problem on CT, while swallowing artefact is also a problem with CT but especially so with MRI because of the long acquisition times. Acquiring CT images with gantry tilt that avoid dental metalwork artefact significantly improves sensitivity in the staging of oral and oropharyngeal tumours.[64]

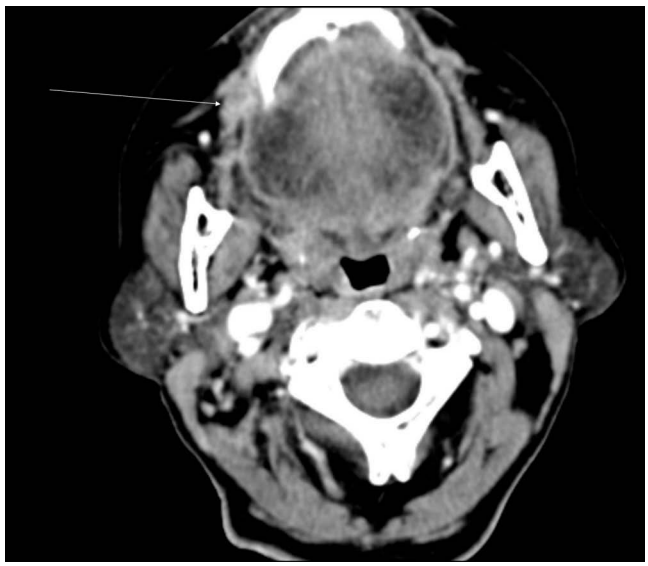


Figure 37.14 Axial contrast-enhanced CT showing right buccal tumour (white arrow).

Various contrast-enhanced CT protocols have been used with a low-flow delayed-phase protocol providing better delineation of the tumour edge compared to a high-flow rate and short-delay protocol but no difference in central tumour enhancement.[65] Intimate apposition of the oral mucosa to the alveolar mucosa makes assessment of small oral tumours particularly difficult with both CT and MRI and cheek puffing has been used as a manoeuvre on CT to separate surfaces.[66, 67] This is not possible with MRI because of long-imaging sequences but the placement of a rolled piece of gauze into the oral vestibule before MRI scanning improves visualization of small tumours.[68]

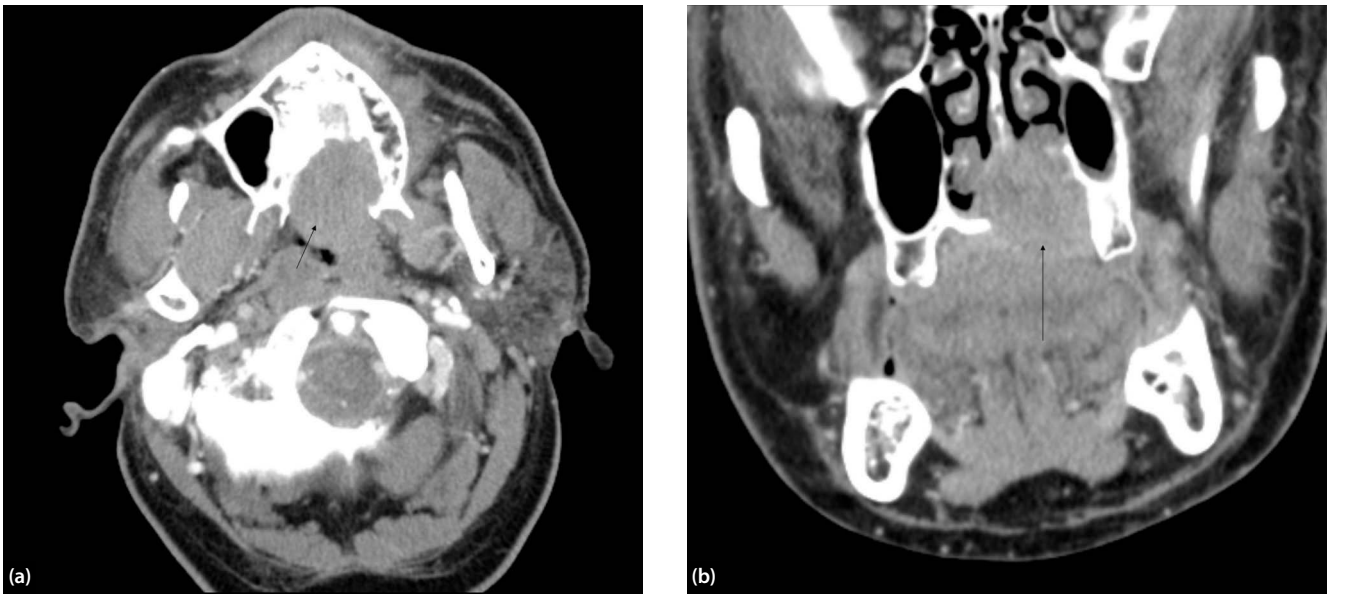


Figure 37.15 Axial **(a)** and coronal reformatted **(b)** contrast-enhanced CT showing left sided destructive hard palate SCC (black arrows) extending into nasal cavity.

MRI is an accurate method for the assessment of oral cavity malignancies, presence of mandibular involvement and the evaluation of depth invasion, with 9.5 mm in one study being the depth cut-off value for determining positive nodes.[69, 70]

In the initial staging of patients with oral cavity tumours, the use of PET with a contrast-enhanced CT is a reliable alternative to the combination of PET/plain CT and a separate diagnostic CT, with a sensitivity of 96% for detecting the primary tumour and a sensitivity of 89% and a specificity of 81% for cervical metastases.[71] An open mouth PET-CT can improve anatomical tumour localization, tumour extent and detection of involvement of adjacent structures when compared to a standard examination.[72] In the study by Seitz et al.[73] PET-CT was not superior to MRI but Baek et al.[74] showed that PET-CT provided further useful clinical information about the primary oral cavity tumour in patients in whom dental artefacts distorted the conventional CT or MRI images. Kim et al.[75] also showed that FDG-PET was more sensitive than CT or MRI in the staging of oral cavity tumours. A SUV nodal maximum of 5.7, either alone or in combination with extracapsular spread, is an independent prognostic indicator for 5-year neck cancer control and survival rates in oral cavity tumour patients with pathologically positive lymph nodes.[76] Furthermore patients with the combination of primary tumour SUV equal to or greater than 19.3 and pathological tumour depth equal to or greater than 12 mm are at greatest risk of poor local control and death.[77] A significant difference has also been shown in maximum SUV on PET-CT between nodes with and without extracapsular spread and a cut-off SUV value of 2.5 is associated with a greater risk of cervical lymph node metastasis.[78] PET and PET-CT however only had a sensitivity of 77.7% and a specificity of 58% in detecting cervical metastases in the primary staging of 473 patients with SCC of the oral cavity.[79] PET-CT and US can be complementary tools in the pre-operative evaluation of patients with SCC of the oral cavity.[80]

Evaluation of whether there is marrow or cortical involvement of the maxilla or mandible by SCC of the oral cavity is crucial for the surgeon to obtain both radical tumour resection and good functional results. In the case of tumours related to the mandible, resection can vary from a shaving of the lingual cortex, rim resection or segmental mandibulectomy. Many surgeons advocate periosteal stripping for tumours adjacent to the mandible at the time of surgery but accurate imaging does help the surgeon plan the treatment options and allows for an informed discussion with the patient prior to surgery. Abd El-Hafez et al. found that PET-CT was more specific than MRI (84% versus 61%) but less sensitive (78% versus 97%) for detection of bone-marrow invasion of the mandible and maxilla, with dental status and tumour origin affecting the diagnostic performance of PET-CT. They concluded that a negative MRI could confidently exclude the presence of bone-marrow invasion while in patients with positive MRI findings, a negative PET-CT was useful in ruling out bone marrow invasion in dentate patients.[81] Gu et al. noted sensitivity, specificity and accuracy of 41.7%, 100% and 84.8% for CT and identical figures of 58.3%, 97.1% and 87% for MRI and PET-CT in the detection of mandibular invasion. The combined use of CT, MRI and PET-CT improved sensitivity to 83.3% without loss of specificity and accuracy but this did not reach statistical significance.[82] Although Vidiri et al. showed that MRI had a higher sensitivity than CT in the assessment of mandibular involvement from SCC of the oral cavity, this did not reach statistical difference.[83] Cone-beam CT (**Figure 36.16**) has been shown to be accurate in predicting bone invasion in patients with oral malignancies, competing well with

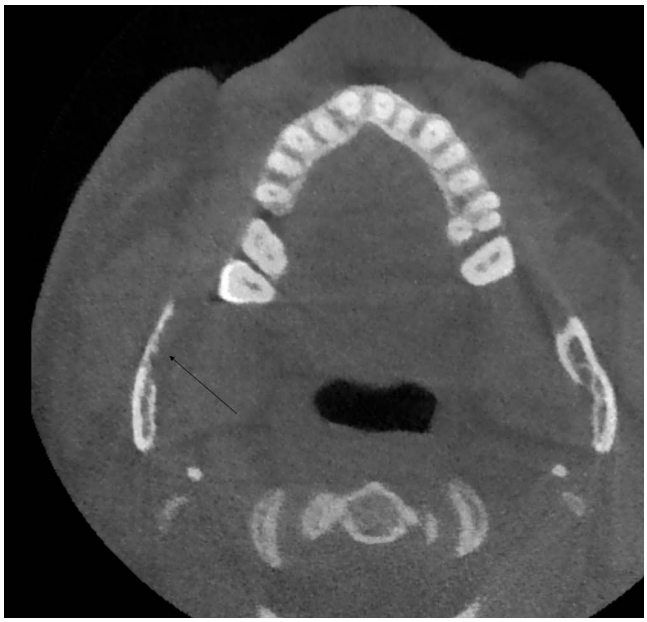


Figure 37.16 Cone-beam CT showing destruction of the inner cortex of the right mandible (arrow) in a histologically proven intraosseous SCC.

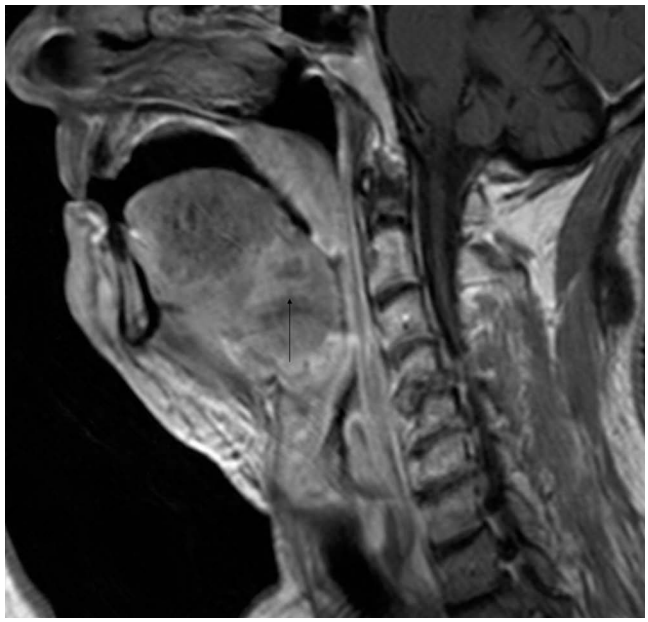


Figure 37.17 Post-gadolinium sagittal T1W MRI showing histologically proven residual tumour (black arrow) six weeks after completing chemoradiotherapy for a large tongue tumour.

CT and single photon emission computerized tomography (SPECT).[84] It therefore appears that CT, MRI and PET-CT all have strengths and weaknesses in assessing bone involvement by SCC and imaging needs to be assessed on a case-by-case basis depending on the site of tumour and local expertise.

Treatment of the clinical N0 neck in SCC of the oral cavity remains a dilemma because of the inability to detect micrometastases on conventional cross-sectional imaging including PET-CT.[85, 86] Although guided FNA seems to correlate best with histological staging for exact N classification compared with CT and PET-CT, it is still not reliable enough to replace elective neck dissection in the N0 neck.[87] The detectability threshold of occult metastases is below the spatial and contrast resolution of CT, MRI and 18FDG–PET in oral cancer patients staged as T1 or T2 and clinically negative neck.[88] Although PET-CT has been shown to perform better than CT or MRI, the sensitivity and specificity of PET-CT in detecting occult cervical metastases varies between 50–64% and 81–97% respectively.[71, 89] There appears to be some value in volume-based PET-CT in patients with clinically node negative oral cancer.[90] Magnetic resonance lymphangiography has limited diagnostic value compared with US with or without fine-needle cytology and CT in the pre-operative staging of the N0 neck.[91] Based on the available evidence, cross-sectional imaging including PET-CT cannot be used in deciding whether to proceed to elective neck dissection or not in N0 patients.

The imaging of post-treatment patients with oral cancer is problematic. The combined use of PET and contrast-enhanced CT for post-treatment monitoring of cancers of the oral cavity has steadily increased in recent years as residual/recurrent disease at the primary site, extent of nodal disease and distant metastases can be assessed. However interpretation of the first follow-up post-treatment PET-CT is challenging and a period of 12 weeks post-treatment is usually recommended to reduce false positive findings.[92, 93] CT or MRI (**Figure 37.17**) rather than PET-CT should be performed during this waiting period of 12 weeks should imaging be required.

OROPHARYNGEAL TUMOURS

The subsites of oropharyngeal tumours include the tongue base and valleculae anteriorly, the tonsils and glossotonsillar sulci laterally, the inferior surface of the soft palate and uvula superiorly and the posterior wall posteriorly.

Tonsillar cancer

Almost all tonsillar tumours originate from the anterior tonsillar pillar (**Figure 37.18**) and commonly spread to the tongue base and soft palate along the palatoglossal muscle and to the pterygomandibular raphe and RMT along the pharyngeal constrictors. Advanced lesions may spread through the pharyngeal wall to the parapharyngeal space (PPS) and along the pharyngeal wall to the nasopharynx superiorly and hypopharynx inferiorly. Once tumour has spread into the PPS it can extend freely to the skull base and into the carotid and masticator spaces.

Tongue base tumours

These tumours are often clinically silent and may spread along the palatoglossal muscle to involve the anterior tonsillar pillar and along the hyoglossal and mylohyoid muscles to the floor of mouth (**Figure 37.19**). Differentiation of

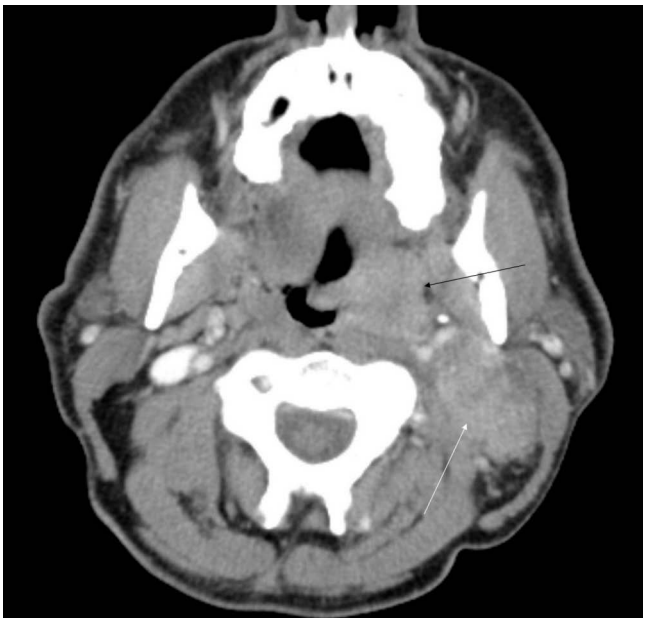


Figure 37.18 Axial contrast-enhanced CT showing large left tonsillar SCC (black arrow) with associated level 2 node (white arrow).

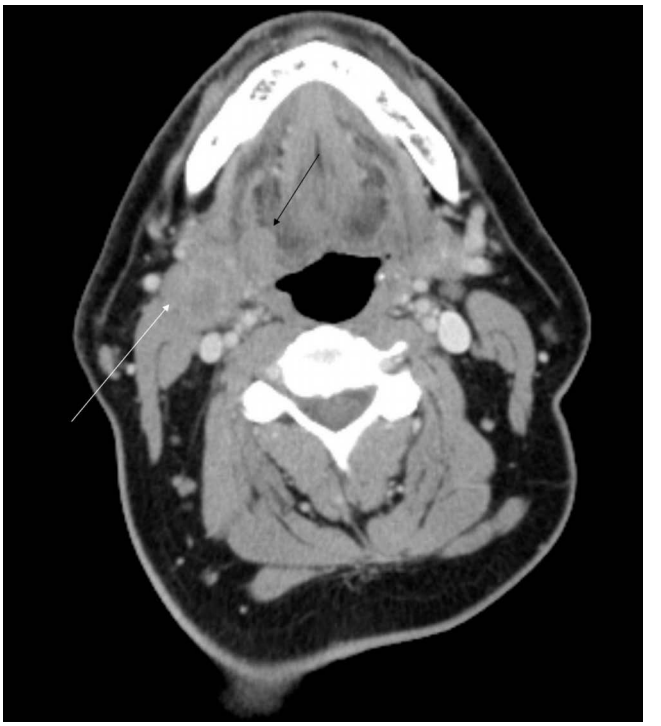


Figure 37.19 Axial contrast-enhanced CT showing right tongue base tumour (black arrow) with associated metastatic right level 2 node (white arrow).

tongue-base tumours from normal lingual lymphoid tissue may be difficult on all cross-sectional imaging.

Soft palate cancer

These tumours usually spread along the tonsillar pillars and in advanced disease on to the nasopharynx.

Posterior oropharyngeal wall cancer

These are rare tumours but more commonly the posterior oropharyngeal wall is invaded by cancers originating from the lateral oropharyngeal wall (**Figure 37.20**). Imaging plays a role in excluding invasion of the prevertebral muscles by demonstrating preservation of the retropharyngeal fat plane with a negative predictive value of 82–97.5% but predicting involvement of the prevertebral space is poor by cross-sectional imaging.[94, 95]

Oropharyngeal tumours spread by direct extension over mucosal surfaces, muscle and bone, along neurovascular bundles and via lymphatic drainage pathways. Imaging needs to evaluate these three routes of spread for accurate staging.[96, 97] Because nodal involvement is the single most important prognostic indicator, accurate assessment of all nodal chains is paramount. Extracapsular spread, detected on imaging by poorly defined nodal margins and surrounding soft-tissue stranding (**Figure 37.21**), is associated with a 3–5-fold increase in local recurrence. US has been shown to discriminate extranodal positive from extranodal negative SCC nodes with comparable accuracy and higher specificity than MRI.[98]

The advantages of staging oropharyngeal tumours with CT are that subtle cortical erosions can be detected

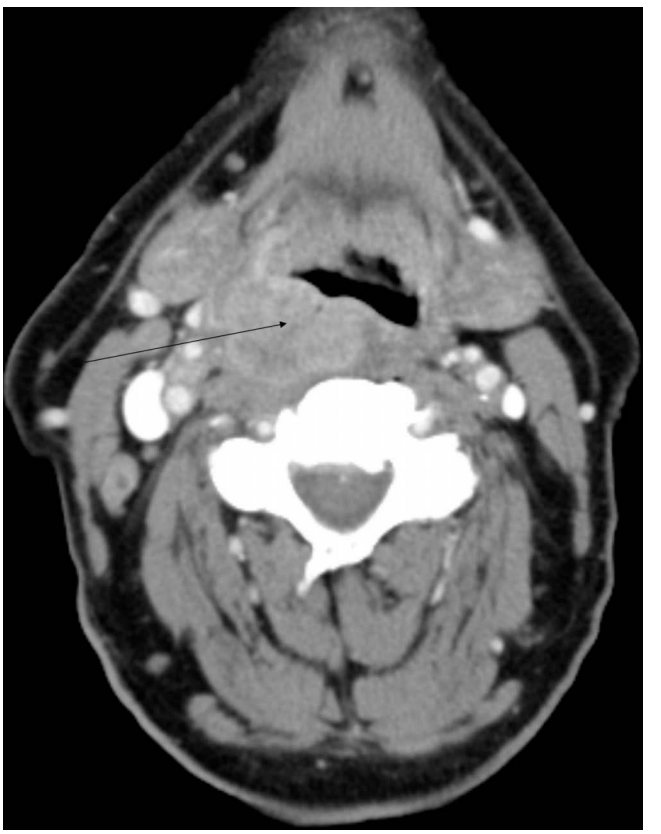


Figure 37.20 Axial contrast-enhanced CT showing large right oropharyngeal tumour involving the posterior oropharyngeal wall (black arrow) and closely apposed to the prevertebral muscles.

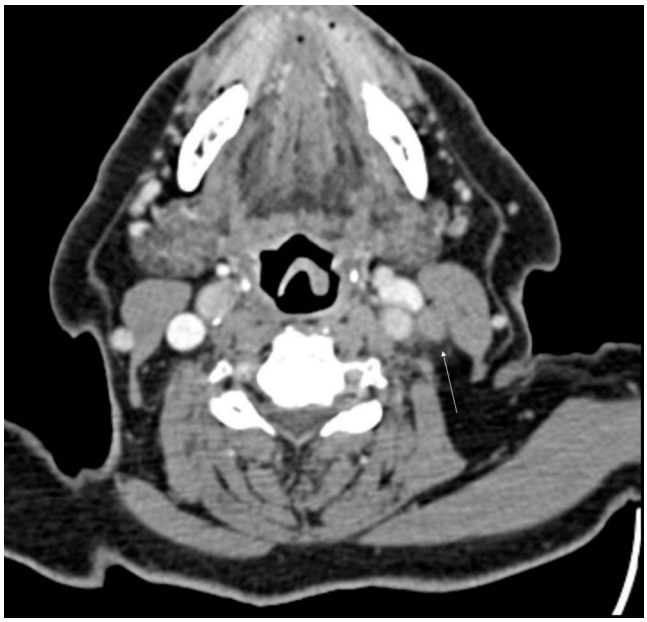


Figure 37.21 Axial contrast-enhanced CT showing a small ill-defined left level 2 node with streakiness to surrounding fat (arrow), histologically confirmed extracapsular spread.

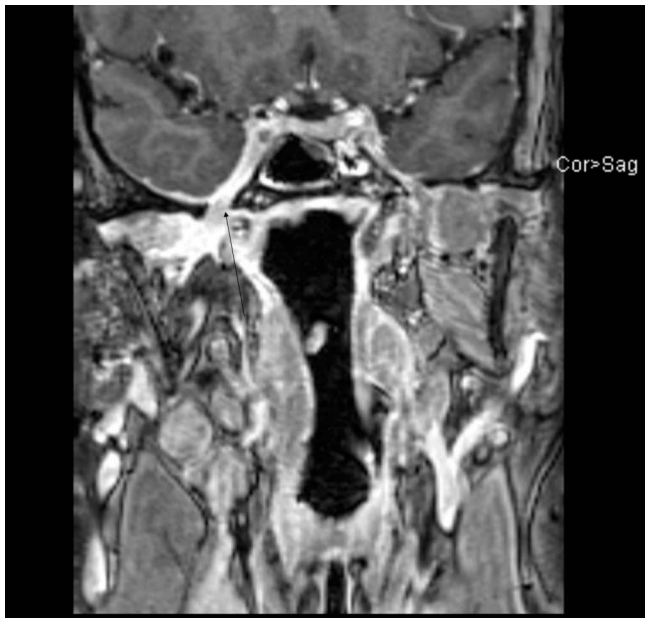


Figure 37.22 Coronal reconstruction of a post gadolinium VIBE (volumetric interpolated brain examination) showing perineural tumour spread along the right mandibular branch of the trigeminal nerve through the foramen ovale (black arrow) and on to the cavernous sinus.

and the chest can be included in the same sitting.[99] MRI is particularly useful in assessing perineural spread (**Figure 37.22**) and bone marrow involvement.[100] It is also an accurate method for measuring tumour invasion depth in the tongue base and this can have a predictive value for nodal metastases, with a cut-off depth of invasion of the tongue base by 14.5 mm for positive nodes.[69]

PET has a higher sensitivity than CT/MRI for detection of primary tumour and cervical metastases but no difference in specificity.[101] The use of a contrast-enhanced CT with conventional PET as a one-step examination has been shown to be a reliable initial staging examination.[71, 102] PET-CT has a higher sensitivity and diagnostic capability than 3T whole body MRI for the detection of distant metastases and second primary tumours.[103, 104] Similarly, PET has been shown to be more sensitive than extended field-multidetector CT for detecting distant metastases albeit with more false positive findings.[105] A pre-treatment PET-CT can be used as a staging tool to aid in treatment planning of SCC of the oropharynx with rates of retropharyngeal and nodal metastases consistent with those in the literature.[106]

Patients often present with a nodal mass and no obvious primary tumour on clinical inspection, the so-called unknown primary, the majority of tumours being in the tonsil and tongue base. PET-CT is particularly good at detecting the unknown primary but is complicated by the normal physiological uptake in these areas (**Figure 37.23**). There is considerable variation in pharyngeal palatine tonsil uptake in normal patients but generally only a small difference between left and right sides and an absolute difference between the maximum SUV between the two sides of 0.83 may be useful in detecting an occult tonsillar carcinoma.[107] Diffusion-weighted MRI is showing some

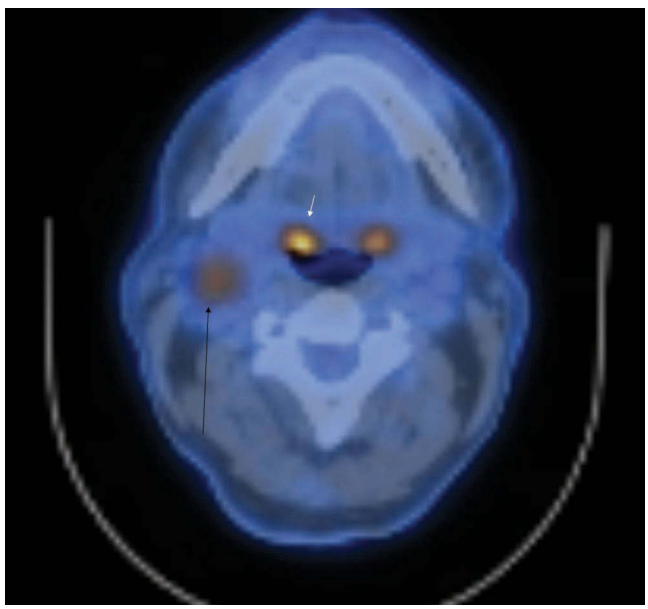


Figure 37.23 Axial-fused PET-CT showing increased activity in the right tongue base (white arrow) in a patient presenting with a right sided neck mass (black arrow) and no apparent primary on clinical examination or conventional CT. Note the normal physiological activity in the left tongue base.

promise in distinguishing between normal lymphoid tissue and SCC of the palatine tonsil.[108]

Oropharyngeal cancer is treated with curative intent by surgery, radiotherapy with or without chemotherapy or a combination of the two. The relationship between tumour volume and local outcome is less pronounced in oropharyngeal cancer compared to other head and neck tumours. However pre-treatment FDG-tumour uptake represents

an independent prognostic factor in patients with oropharyngeal SCC and patients with high FDG uptake may be better treated by surgery followed by radiotherapy with or without chemotherapy.[109] Perfusion CT provides a rapid, reliable and non-invasive technique for assessing tumour vascularity and may predict response to induction chemotherapy and mid-term remission-free survival in patients with advanced oropharyngeal SCC.[110] Treatment of the clinical N0 neck in T1 and T2 oropharyngeal cancer, as in oral cancer, remains a dilemma as CT, MRI and PET-CT all fail to detect the presence of lymph node micrometastases reliably.[86–90]

Response to definitive treatment with radiotherapy with or without chemotherapy is a powerful predictor of outcome.[111] In the post-therapy setting in patients with oropharyngeal cancer, imaging with PET-CT can have considerable influence on clinical decision-making as early detection of residual disease/recurrence enables salvage surgery to be carried out as soon as possible while neck dissection is only performed if there is evidence of residual nodal disease.[112, 113] Accurate assessment of response to treatment is therefore essential to optimize the chance of cure in those patients with residual disease and to minimize unnecessary surgery in patients who have been successfully treated. Several studies have shown that the use of PET-CT is superior to conventional imaging in response assessment as small residual nodes are common following treatment and radiation-induced changes are difficult to distinguish from residual disease using CT or MRI.[114, 115] The sensitivity of PET for detecting residual or recurrent cancer is high, in the range of 84–100%.[116, 117] The timing of PET-CT after treatment is critical to accurately differentiate residual disease from inflammatory changes secondary to treatment and thereby increase specificity. PET-CT performed between 12 and 16 weeks post-treatment has high diagnostic accuracy of response assessment.[118, 119] Should disease progression be suspected in the immediate post-treatment period, then contrast-enhanced CT or MRI and not PET-CT should be performed.[93] Diffusion-weighted MRI 2–3 weeks after completion of treatment has the potential to allow prediction of treatment response at the primary site.[13, 120, 121]

Regular surveillance is especially important in the first 2 years after treatment since the vast majority of disease recurrences are found during this period and PET combined with contrast-enhanced CT can be performed when there is a suspicion of recurrence.[118, 122, 123] However, there does not appear to be a role for blanket surveillance PET-CT at 12 and 24 months for detecting recurrence.[124]

HYPOPHARYNGEAL TUMOURS

Hypopharyngeal cancers are usually SCC and have the worst prognosis among head and neck cancers. They are insidious tumours, commonly presenting with a lump in the neck, secondary to metastatic nodal involvement, or dysphagia, otalgia, weight loss and hoarseness when the recurrent laryngeal nerve is involved. The trend of these tumours to spread in a submucosal fashion makes accurate delineation by cross-sectional imaging of paramount importance in planning treatment. The most important features determining prognosis are the size and local spread of the primary tumour and the extent of nodal involvement.[125]

The hypopharynx extends from the oropharynx to oesophageal verge and is divided into three regions, pyriform sinus or fossa, post-cricoid region and posterior hypopharyngeal wall, with distinct spread patterns of tumours in each region. Tumours arising from the lateral aspect of the pyriform sinus (PS) invade the posterior aspect of the thyroid cartilage and can extend into the paraglottic space and soft tissues of the lateral compartment of the neck (**Figure 37.24**). Tumours arising from the medial aspect of the PS show early laryngeal invasion. Posterior hypopharyngeal tumours (**Figure 37.25**) tend to grow in a cranio-caudal direction while tumours in the post-cricoid region (**Figure 37.26**) tend to invade the posterior aspect of the larynx.

The important points in staging are evaluating all the hypopharyngeal subsites, the larynx, thyroid cartilage, nodal status, distant metastases and any other synchronous primary, especially oesophageal carcinoma.[104, 126,] Imaging usually results in upstaging the tumour.[127, 128] Contrast-enhanced CT performed during quiet breathing is the preferred method of evaluating the hypopharynx due to its shorter acquisition time, facility for multiplanar reconstruction and ability to assess the chest and abdomen in one sitting. Three-dimensional CT laryngography with modified valsalva manoeuvre is informative for the diagnosis of PS apex involvement.[129] CT has also been shown to be a reliable method for assessing tumour volume with CT-based tumour volume being a predictor of outcome after treatment with both radiotherapy and surgery.[130–132]

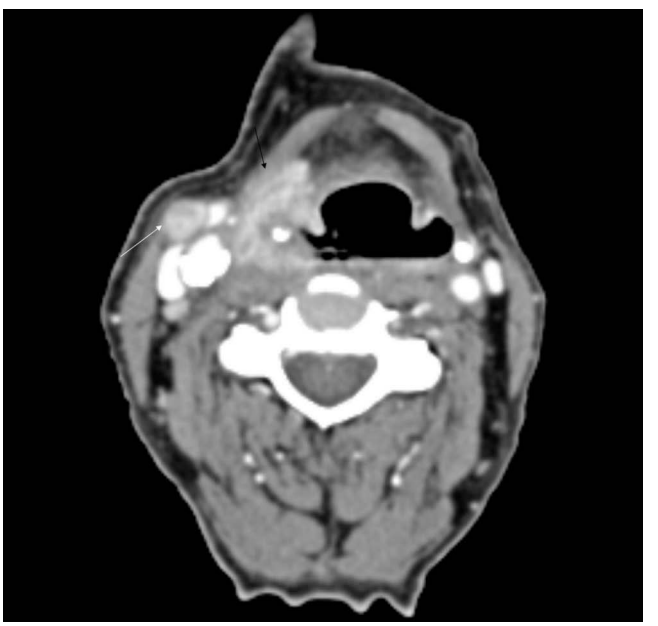


Figure 37.24 Axial contrast-enhanced CT showing right pyriform fossa tumour just extending into the paraglottic space and extralaryngeal soft tissues (black arrow) with associated metastatic level 3 node (white arrow).

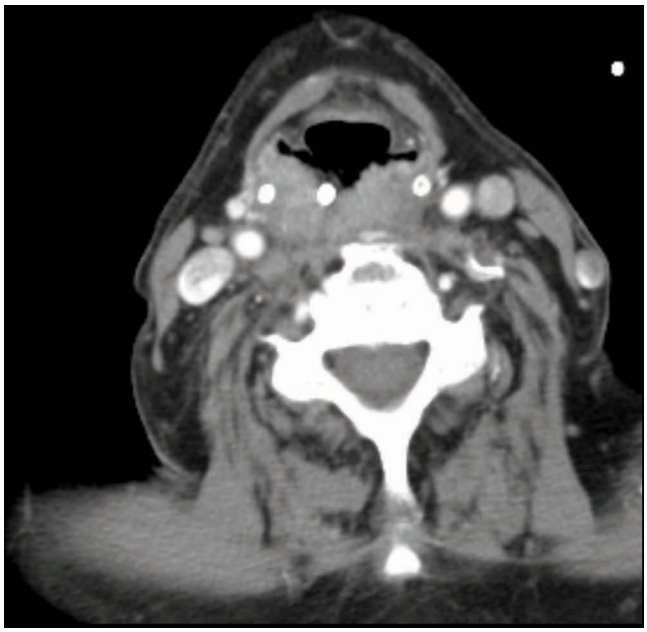


Figure 37.25 Axial contrast-enhanced CT showing a large hypopharyngeal posterior wall tumour extending on to the prevertebral muscles.

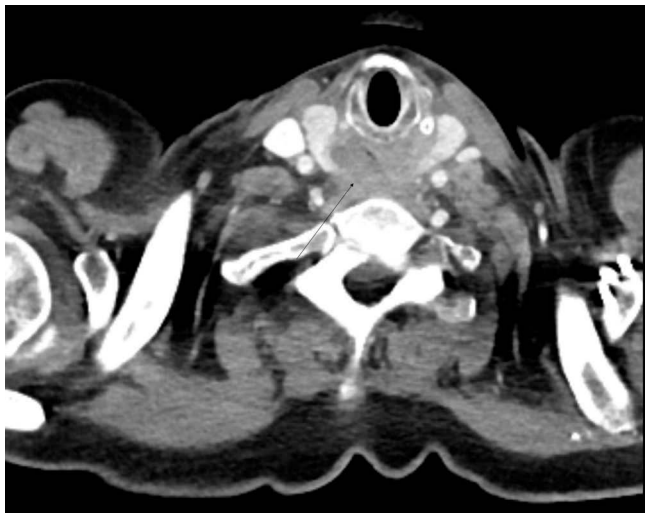


Figure 37.26 Axial contrast-enhanced CT showing a post-cricoid carcinoma (black arrow) extending on to the prevertebral muscles.

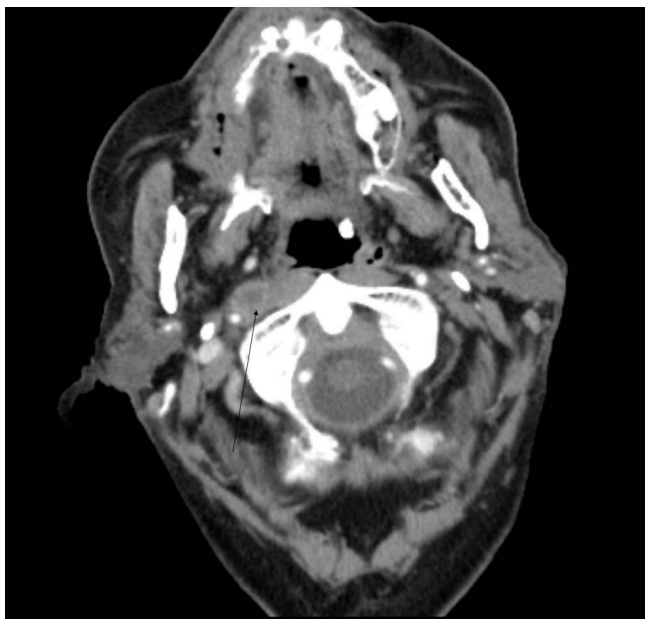


Figure 37.27 Axial contrast-enhanced CT showing a necrotic right retropharyngeal node (black arrow) in a patient with a hypopharyngeal posterior wall tumour.

Correct assessment of nodal status is essential as hypopharyngeal cancer has a high risk for early regional lymph node dissemination and metastatic nodal disease still remains the single most important negative predictor. CT perfusion has been suggested as a way of distinguishing malignant from non-malignant nodes.[133] Deng et al. noted a regional lymph node metastatic rate of 73.9% on CT/MRI images in 88 patients with hypopharyngeal cancer, the highest rates being at level 2 and 3, with bilateral disease a potential risk factor for retropharyngeal node metastases.[134] Tumours originating from the posterior wall of the hypopharynx not only show a significantly higher incidence of retropharyngeal nodal metastases (**Figure 37.27**) as demonstrated by CT and/or MRI than other subsites but have a high incidence of distant metastases resulting in dismal outcomes.[135] FDG-PET has been shown to be helpful in detecting retropharyngeal nodal metastases in hypopharyngeal cancer, which should be suspected in patients with tumours originating from the posterior pharyngeal wall and those with ipsilateral level 5 lymph node metastases.[136]

PET-CT in hypopharyngeal cancer, just as in oropharyngeal cancer, has a higher sensitivity than 3T-MRI or CT for the detection of distant metastases and second primary tumours.[103–105] PET-CT has a high sensitivity for detection of residual and recurrent tumour following surgery and radiotherapy.[125]

LARYNGEAL TUMOURS

Laryngeal carcinoma is the commonest head and neck malignancy, comprising 30–40% of all cases, the vast majority being SCC. Most laryngeal tumours present with hoarseness and less commonly with a neck mass, dysphagia, stridor or haemoptysis. Around 80% of tumours are glottic, arising from the vocal cords, 15% are supraglottic, arising from epiglottis, false cords or aryepiglottic fold (**Figure 37.28**) and 5% subglottic. Some tumours are transglottic involving all laryngeal levels (**Figure 37.29**). Although most laryngeal tumours are mucosal lesions and easily seen endoscopically, cross-sectional imaging frequently demonstrates the limitations of clinical and endoscopic examination in evaluating submucosal disease and cartilage invasion.

Imaging is important to identify the site and size of primary tumour, involvement of laryngeal cartilage and surrounding extralaryngeal structures, state of airway and nodal status.[127, 137–140] Multidetector CT is the preferred modality for evaluating laryngeal carcinoma given its widespread availability and ease of acquisition with

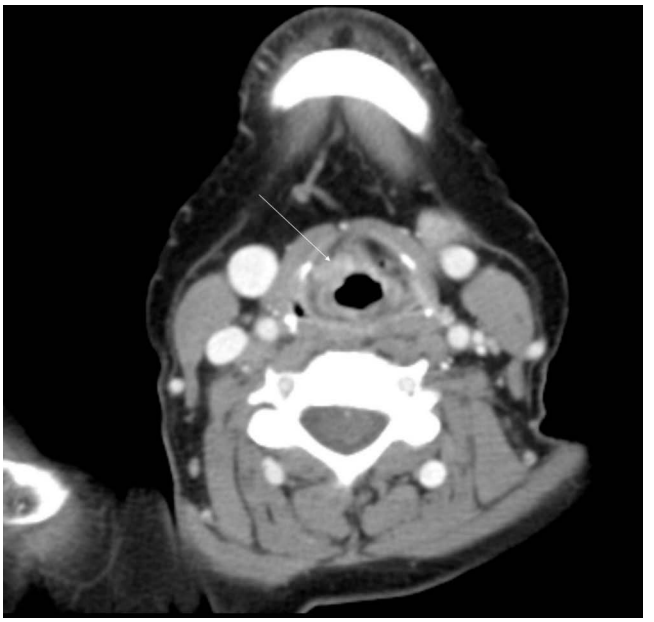


Figure 37.28 Axial contrast-enhanced CT showing a supraglottic tumour (white arrow) involving the epiglottis and right paraglottic space.

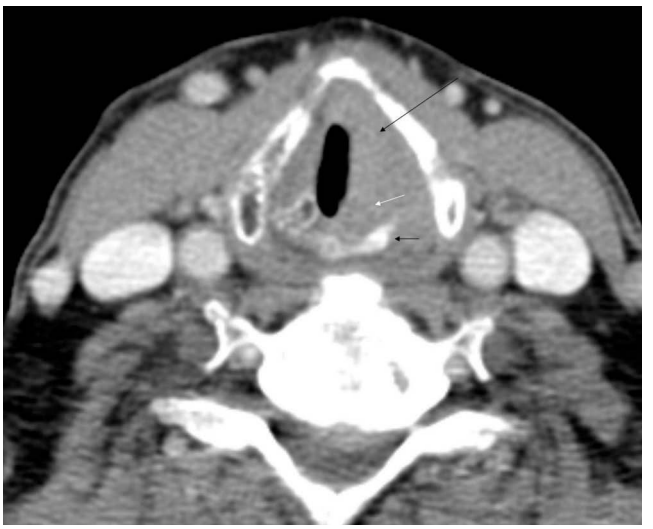


Figure 37.29 Axial contrast-enhanced CT showing a large left transglottic tumour (long black arrow) with completely destroyed left arytenoid (white arrow) and sclerotic left cricoid cartilage (short black arrow).

excellent multiplanar reformation while ultrasound, MRI and PET-CT are used as problem-solving tools. Functional imaging of the larynx on multidetector CT in the form of inspiration, phonation and valsalva and virtual laryngoscopy have a questionable role in staging.[141–143] The pretreatment staging accuracy of laryngeal carcinoma by CT has been reported to be between 84.9% and 88.8% on recent studies with problems in distinguishing tumour from peritumoral inflammation, identifying small tumours and predicting cartilage invasion.[142, 144–148] Incomplete ossification of the thyroid cartilage and asymmetric mineralization of the arytenoids make cartilage assessment difficult but the presence of tumour on both sides of the cartilage is said to be a useful imaging finding in predicting cartilage involvement.[149, 150] No statistical difference was seen in a study of 34 patients with laryngeal cancer between MRI and post-surgical pathohistology in tumour extension to the anterior commissure, pre-epiglottic space and subglottis as well as cartilage infiltration but paralaryngeal infiltration was overdiagnosed by MRI resulting in a correct T classification in 76% of those cases.[151] MRI overpredicts thyroid cartilage involvement although there is some evidence that contrast-enhanced MRI may differentiate inflammatory from neoplastic change and demonstrating a normal cartilage signal on MRI is reassuring.[152, 153] MRI is therefore more sensitive but less specific than CT in detecting neoplastic cartilage invasion.

In view of the sensitivity and specificity issues with CT and MRI, US (**Figure 37.30**) is being increasingly used as

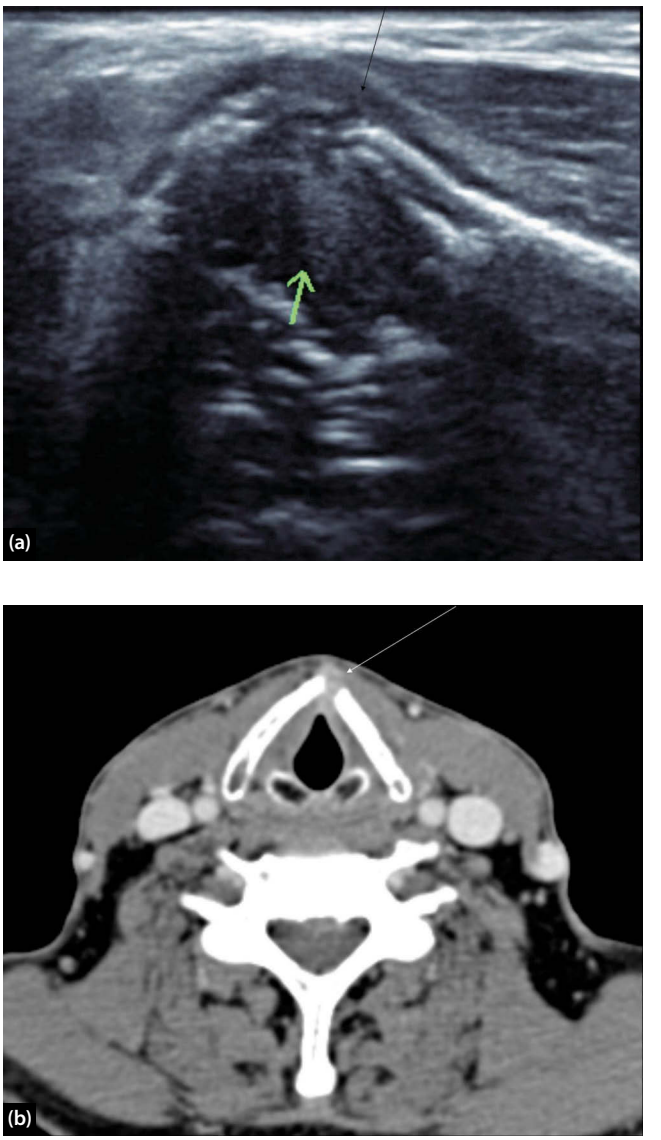


Figure 37.30 US of the larynx (a) showing a sizeable low reflectivity laryngeal tumour (thick arrow) extending through a defect in the thyroid cartilage (black arrow) with the corresponding contrast-enhanced axial CT **(b)** confirming extralaryngeal spread of tumour (white arrow).

a complementary technique in the evaluation of laryngeal cancer, which usually appears hypoechoic on ultrasound.[153] Hu et al. demonstrated an accuracy of 83.3% for US compared to 88.8% for CT and an accuracy of 80% for US compared to 76.5% for unenhanced MRI in the T-staging of glottic cancer, with US only being inferior in demonstrating tumour involvement in the retrolaryngeal structures.[145, 154, 155]

The performance of PET-CT not surprisingly is better than stand-alone PET or CT in patients with cancer of the larynx and can have a major impact on management.[156] However, as in the case of other head and neck tumours, it has no role in predicting the need for surgical neck dissection in the N0 neck.[157, 158]

The treatment of laryngeal cancer consists of surgery including laser resection, total or partial removal of the larynx and radiation therapy, either as a cure or as an adjunct after radiotherapy. Conservative laryngeal surgery preserves a portion of the larynx so that a voice can be produced while obtaining the same local control as that provided by total laryngectomy. Appreciating the normal imaging findings following both partial and total laryngectomy is important in the interpretation of cross-sectional imaging.[159–161] Hemithyroidectomy used to be performed as part of total laryngectomy but this practice is now being questioned and pre-operative evaluation of any thyroid gland involvement is essential in deciding whether to preserve the thyroid gland. [162] Laryngeal oedema following radiotherapy is common, particularly affecting the supraglottis, and may mask recurrence.[163]

Imaging for recurrence following treatment to laryngeal cancer includes CT, MRI and PET-CT.[164] PET-CT is useful in detecting local residual tumour after treatment and has been suggested as a cost-effective means of selecting patients for direct laryngoscopy in suspected recurrence following radiotherapy.[165–167] PET-CT however has too high a false negative rate to warrant deferring neck dissection in the N0 neck in suspected recurrence following treatment.[168]

Lymphoma is a rare tumour of the larynx that classically presents as a large uniformly enhancing submucosal mass showing no necrosis centred in the supraglottis that extends into the glottis. Cervical adenopathy is not usually present and as in SCC, lymphoma may extend into the subglottis, pharynx and laryngeal cartilages.[169, 170] Sarcomas make up about 0.3–1% of all laryngeal malignancies of which chondrosarcomas show specific imaging findings with an expansile defect in either the thyroid or cricoid cartilages (**Figure 37.31**).

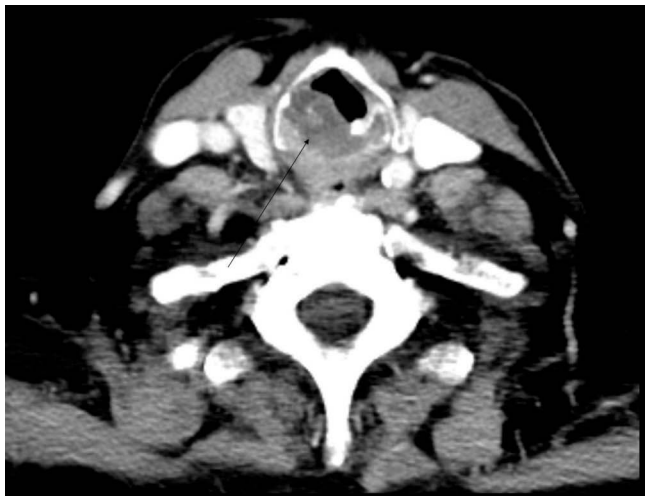


Figure 37.31 Axial contrast-enhanced CT showing low grade chondrosarcoma (black arrow) centred around an expanded and remodelled right cricoid cartilage.

NECK LUMPS

The imaging of patients presenting with a neck lump depends on the age of the patient, clinical history and location of the mass.

The majority of neck lumps in children are simply due to reactive lymph nodes secondary to an upper respiratory tract infection, earache or toothache and if small, soft and mobile and associated with an upper respiratory tract infection will usually regress within 3 weeks. In such cases, no imaging is required and the parents are simply reassured and asked to return if the child becomes systemically unwell or if the swelling increases in size. Children with fever, hepatosplenomegaly, weight loss or night sweats and nodes greater than 3 cm should have a chest X-ray, screening blood tests including a full blood count and serology especially for Epstein–Barr virus, and the neck imaged initially by ultrasound.[171] As a general rule, US will differentiate reactive lymphoid hyperplasia from lymphoma and identify abscess formation within nodes[172] and excision biopsy is necessary in only a very small proportion of cases.

Adult lymphadenopathy is more unusual than in children and any adult presenting with a suspicious neck lump should be imaged by US initially and if this appears suspicious or the entire deep extent cannot be ascertained, then CT or MRI are necessary.[173]

In the non-lymphadenomatous neck swellings, can US differentiate between a cystic or solid mass with CT and MRI serving as supplementary examinations in defining the exact anatomy prior to any surgery. The vast majority of cystic masses in children are congenital or developmental in origin and in adults inflammatory or malignant.

Thyroglossal duct cyst (TDC)

This is the most common congenital cystic mass and the second most common benign mass after benign lymphadenopathy. The thyroid primordia migrate down the neck along the thyroglossal duct which runs from the foramen caecum in the base of the tongue to the lower anterior neck and normally involutes in the 8th–10th week of gestation. If any portion of the duct persists, secretions from the epithelial lining may give rise to cysts and as the duct is intimately related to the hyoid bone, most occur either below (65%) or at the level of hyoid bone (15%). Seventy-five per cent of cases occur in the midline and the rest up to 2 cm off the midline.

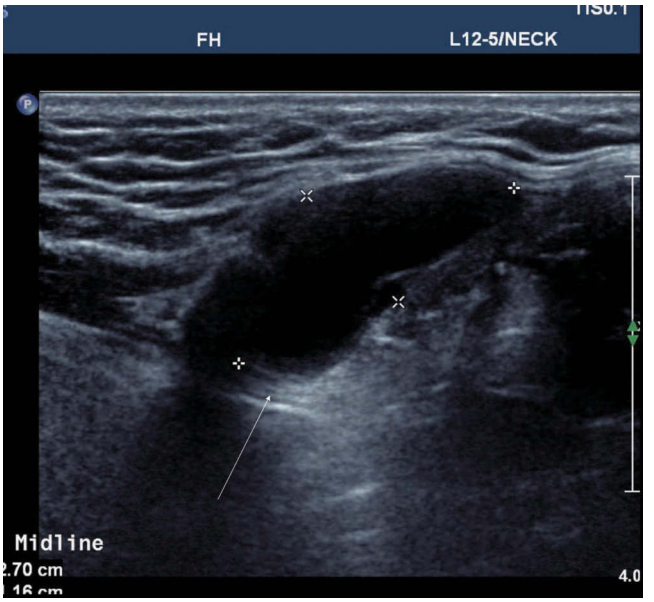


Figure 37.32 US showing a midline infrahyoid homogenous anechoic cystic mass with posterior wall enhancement (black arrow) in keeping with a thyroglossal duct cyst.

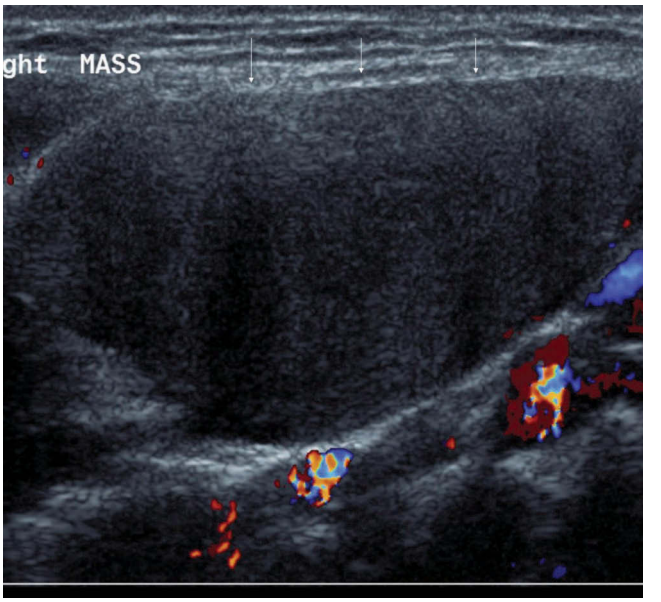


Figure 37.33 US showing an avascular, pseudosolid right level 2 mass in keeping with a second branchial cleft cyst.

On US TDCs (**Figure 37.32**) have a varied appearance ranging from a homogenous anechoic mass with posterior wall enhancement, a pseudosolid mass due to proteinaceous secretions or a mass with a heterogenous echo pattern due to previous haemorrhage or infection. A variable appearance is also seen on CT or MRI depending on the cyst contents but on MRI the cysts are invariably of high T2 signal and variable T1 signal depending on the amount of proteinaceous secretions.

The important imaging points are the relationship of the TDC to the hyoid bone, the presence or absence of normal thyroid tissue and whether any solid material is present within the cyst as there is a 1% incidence of carcinoma, classically papillary thyroid cancer (PTC) within TDC.

Second branchial cleft cyst (BCC)

Second BCCs account for 95% of all branchial cysts, typically occur between 10 and 40 years and classically present as a mass at the angle of the mandible superficial to the carotid sheath, posterior to the submandibular gland and along the anteromedial border of sternomastoid.

The sonographic appearances of second BCCs (**Figure 37.33**) is variable ranging from a classic anechoic simple cyst with posterior wall enhancement to a pseudosolid or heterogenous mass with internal debris and septae.[174] If on US a beak is identified pointing medially, then CT or MRI is warranted to exclude a sinus or fistula. On CT, classic second BCCs appear as homogenous low-attenuation masses with a thin wall and on MRI as masses of high T2 and low T1. On all imaging modalities, BCCs complicated by previous infection or haemorrhage appear as ill-defined, heterogenous, thick-walled masses containing debris and septae (**Figure 37.34**). Such a mass can cause confusion as a completely necrotic node from a head and neck SCC or a PTC may mimic BCC. If the patient is over 40, a smoker and drinks excessive alcohol, then such a mass has to be considered to be a metastatic SCC till proven otherwise and if a primary tumour is not identified clinically or by CT/MRI, then consideration should be given for PET-CT. In a younger patient, the mass is likely to represent a BCC or PTC and it is essential to look for other cystic masses especially around the thyroid gland as the primary tumour is often very small and not necessarily picked up by imaging.[175]

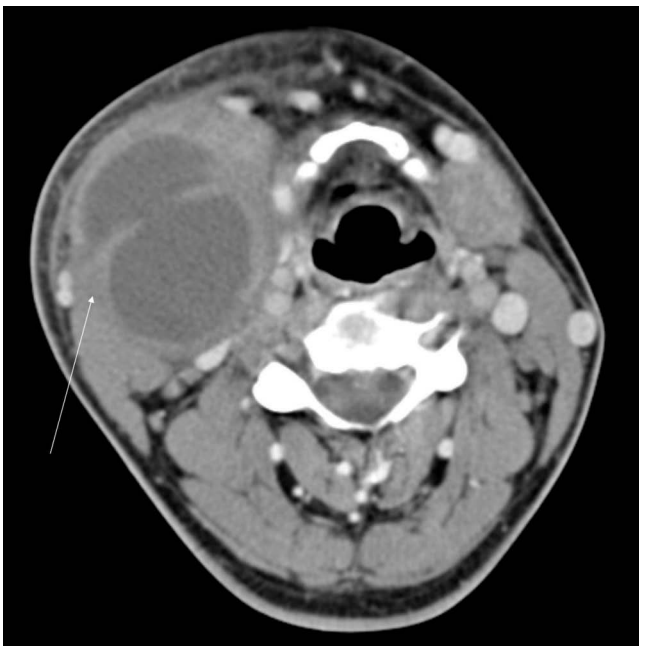


Figure 37.34 Axial contrast-enhanced CT showing a septated thick-walled right level 2 mass (white arrow) displacing the submandibular gland anteriorly and deep to sternomastoid in keeping with an infected second branchial cleft cyst.

Epidermoid/dermoid cyst

The difference between these two entities is histological, the more common dermoid cyst containing skin appendages such as sebaceous glands and hair follicles while an epidermoid cyst is entirely ectodermal. Epidermoids tend to present in infancy with dermoid cysts presenting later and both frequently occur in the submental or suprasternal regions in or close to the midline. These masses are usually well defined on imaging and may have a varied appearance on US (**Figure 37.35a**) varying from an anechoic mass with posterior wall enhancement to a pseudosolid appearance. Fatty content is pathognomic for a dermoid but in its absence, differentiation by imaging is not possible.[176] On CT the central cavity is usually filled with homogenous low-attenuation material (**Figure 37.35b**) but may appear to contain 'marbles' due to fat coalescing into small nodules within the fluid.

Ranula

This is a retention cyst resulting from obstruction of the duct to the sublingual gland and may be simple when confined to the floor of mouth or plunging when extending into the submandibular space. On US a simple ranula appears as a unilocular, well-defined cystic mass in the submental region related to the sublingual gland. It may contain fine internal echoes usually due to the presence of debris from previous episodes of inflammation.[177] On CT a simple ranula will appear as a solitary, low-attenuation, non-enhancing thin-walled mass and on MRI a mass of low T1 and high T2 signal. A plunging or diving ranula (**Figure 37.36**) forms from a ruptured ranula that extends either dorsally or caudally through defects in the mylohyoid muscle, the so-called boutonniere anomaly, into the submandibular space. As these plunging ranulas are effectively pseudocysts, there is usually some associated granulation tissue and may show enhancement on CT or MRI.

Salivary and thyroid gland masses

These will be discussed elsewhere in this section.

Lipoma

The head and neck is a typical site for lipomata which characteristically present as striped or feathery masses on ultrasound, masses of similar low attenuation as the surrounding fat on CT (**Figure 37.37**), and as masses of high T1 and T2 signal and low on fat suppression sequences on MRI.

Nerve sheath tumours

Nerve sheath tumours such as neurofibromas and schwannomas (**Figure 37.38**) may mimic lymph nodes on US as they can appear as diffusely hypoechoic masses with marked vascularity. They can also undergo cystic degeneration and then mimic cystic metastatic nodes.

Vascular malformations

Low-flow vascular malformations are common in the head and neck and comprise venous and lymphatic malformations or a combination of the two.

Venous malformations especially haemangiomas (**Figure 37.39**) are commonly found in the masticator space especially within the masseter muscle and phleboliths are seen in 22% of cases. The aim of imaging is to identify the extent of the lesion and the exact anatomical location.[178, 179] US usually suggests the diagnosis and further cross-sectional imaging is needed to ascertain its extent.

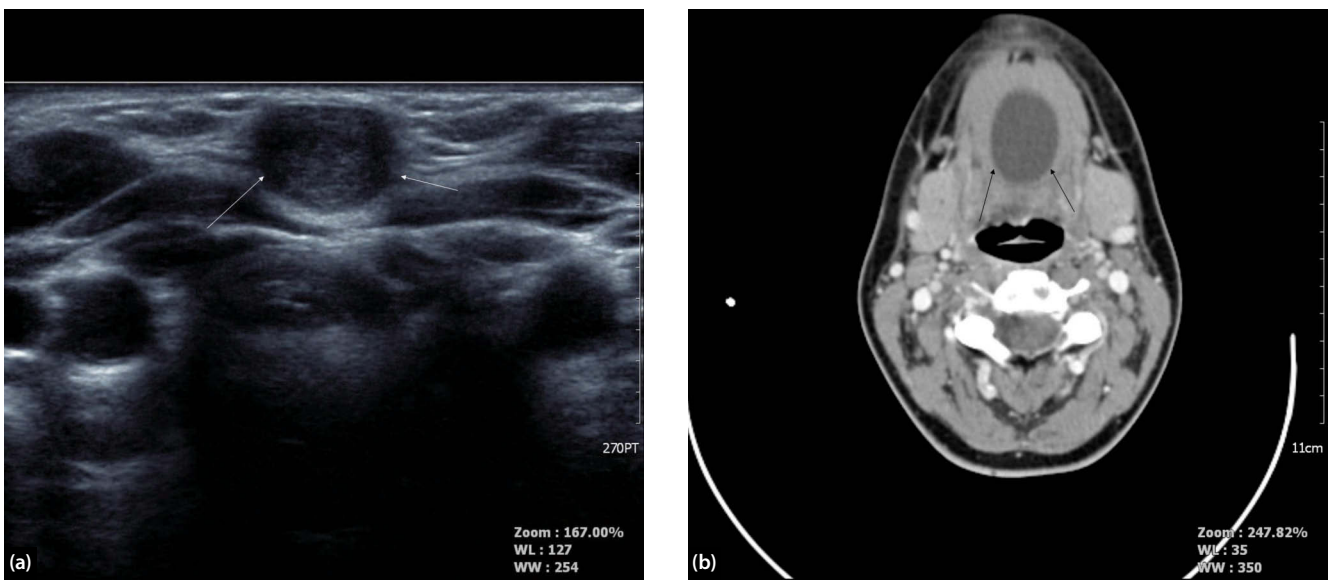


Figure 37.35 US **(a)** showing a midline, infrahyoid mass containing internal echoes (white arrows) in a child, a histologically confirmed dermoid and contrast-enhanced axial CT **(b)** showing a midline cystic floor of mouth dermoid (black arrows) in an adult.

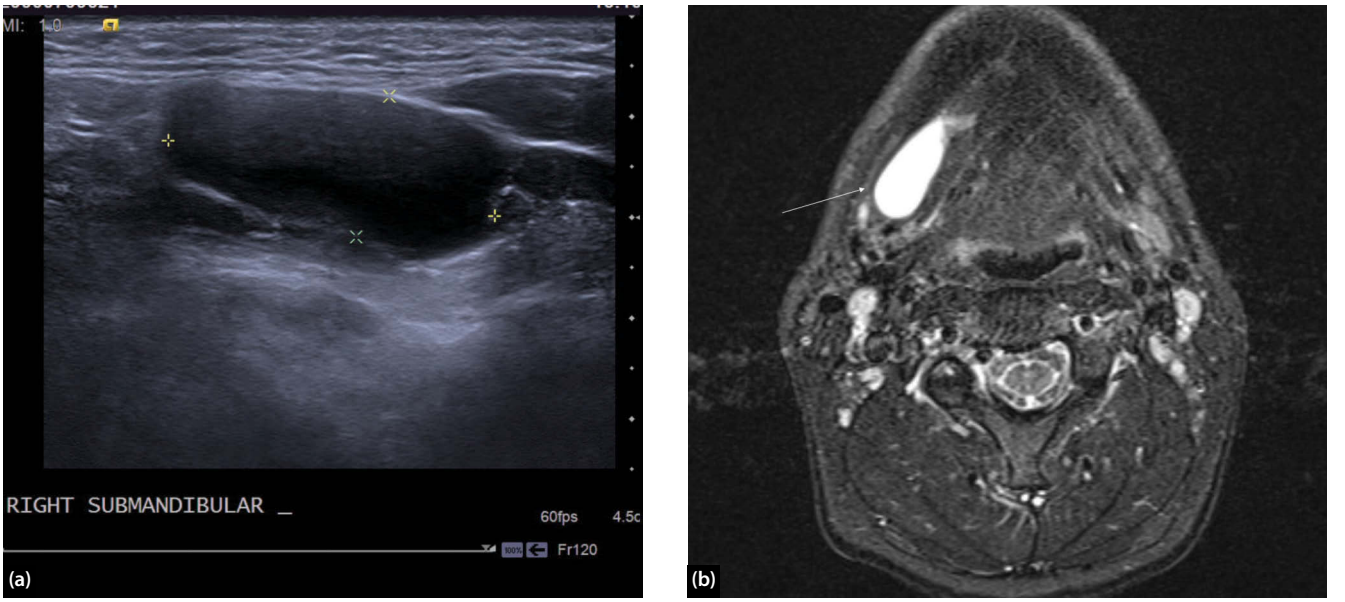


Figure 37.36 US **(a)** and axial STIR (short tau inversion recovery) MRI **(b)** of a cystic plunging ranula (white arrow) extending into the right submandibular space.

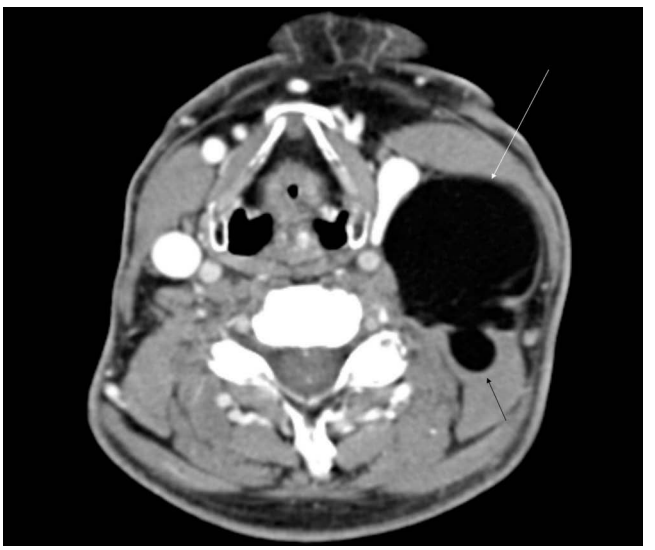


Figure 37.37 Contrast-enhanced axial CT showing a large lipoma deep to left sternomastoid (white arrow) and compressing the jugular vein. Note the small intramuscular component of the lipoma (black arrow) extending into levator scapulae.

US appearances are characteristic with the lesion showing a low reflectivity heterogenous echo pattern with multiple sinusoidal spaces. On MRI (**Figure 37.40**) venous vascular malformations show a striking high signal on T2-weighted sequences, including short tau inversion recovery (STIR). MRI is not as sensitive as CT or US in detecting phleboliths but shows the entire extent of the malformations very eloquently.

Lymphatic malformations or lymphangiomas are congenital abnormalities that arise when developing lymphatics fail to establish communication with developing veins.[180] The most common lymphangioma, also called cystic hygroma, typically presents in childhood as a

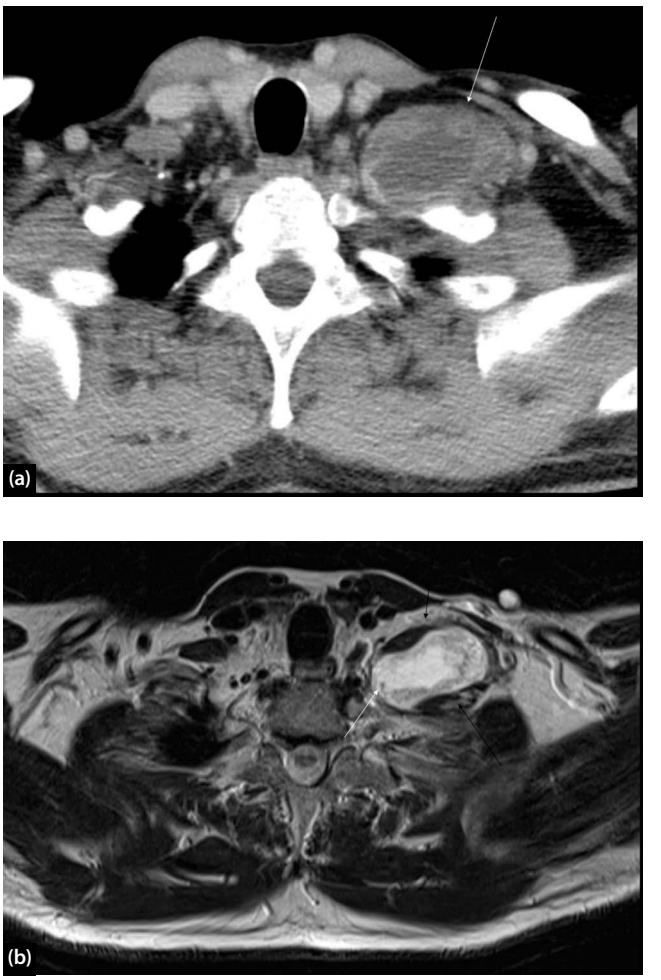


Figure 37.38 Contrast-enhanced axial CT (a) and T2 weighted axial MRI **(b)** showing left interscalene groove schwannoma (white arrows) arising from one of the branches of the brachial plexus.

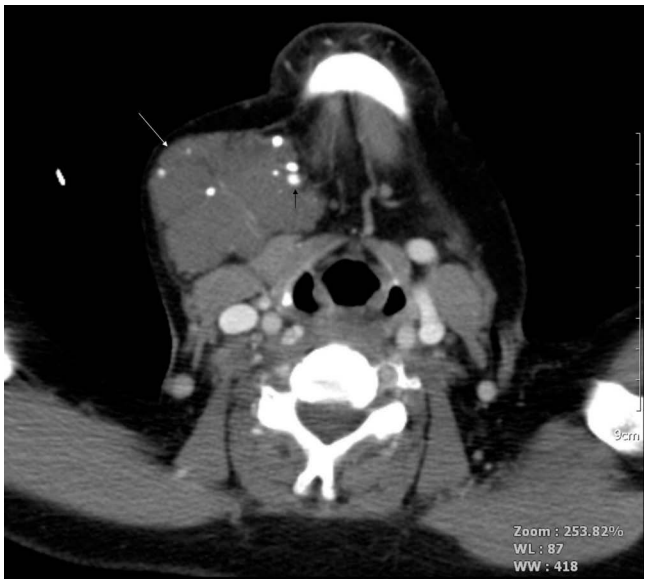


Figure 37.39 Contrast-enhanced axial CT showing a non-enhancing haemangioma (white arrow) containing several foci of calcification (black arrow) in the right submandibular space.

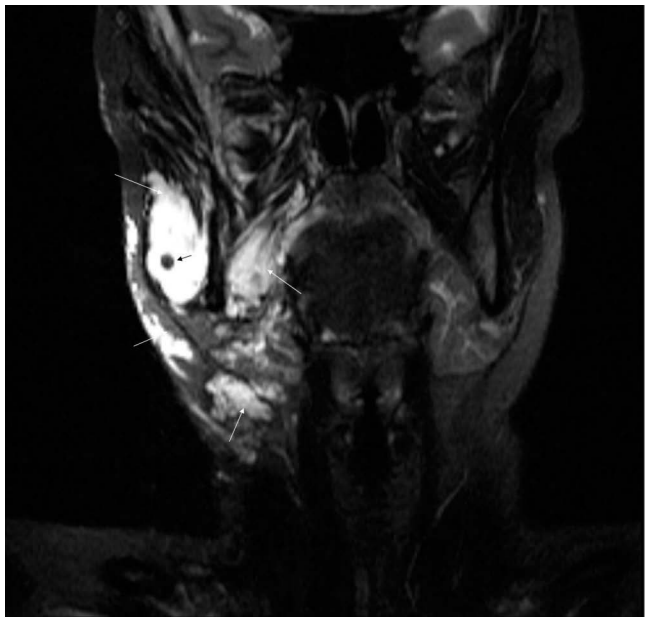


Figure 37.40 Coronal STIR (short tau inversion recovery) MRI showing a multifocal low-flow vascular malformation in the right side of neck involving the skin and several different spaces (white arrows) with a small plebolith (black arrow) within the masseteric component.

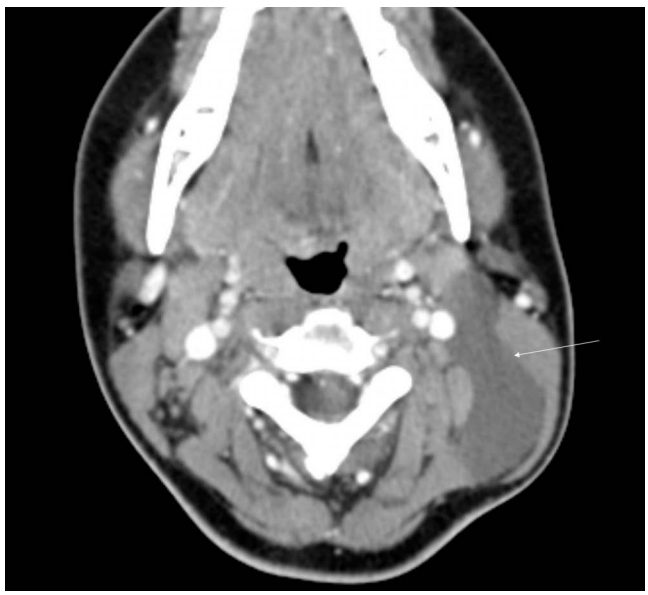


Figure 37.41 Axial contrast-enhanced CT showing a lymphangioma (arrow) within the left lateral compartment of neck deep to sternomastoid and abutting the internal carotid artery.

posterior triangle mass. Imaging usually reveals a multiloculated mass with septa of variable thickness that invaginates between vessels and other normal structures to occupy multiple contiguous spaces (**Figure 37.41**).

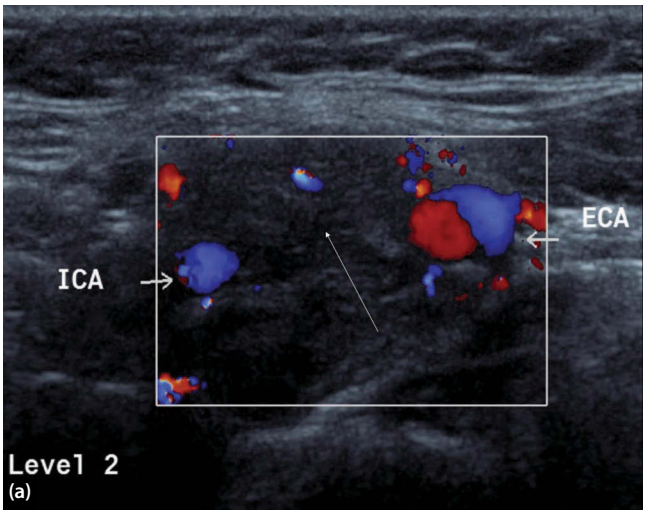
Paragangliomas

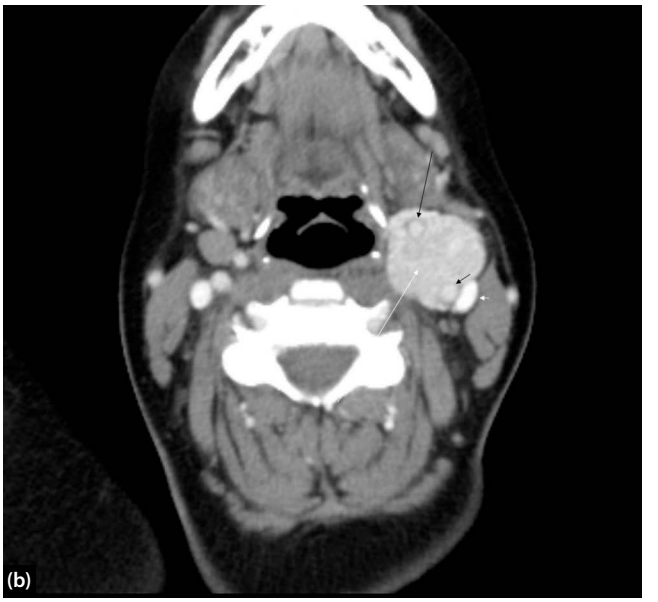
Paragangliomas are benign vascular tumours derived from primitive neural crest and occur anywhere along the carotid sheath as far as the skull base, the most common being the carotid body tumour (CBT).[181] CBT occurs at the bifurcation of the common carotid artery with resultant characteristic splaying of the internal and external carotid arteries (**Figure 37.42**). As the tumour increases in size, it may encase the carotid vessels but does not narrow their calibre.[182] Because of its site a CBT can be mistaken for an abnormal lymph node in the upper cervical chain. Other common paragangliomas are the glomus jugulare and glomus vagale arising from the jugular vein and vagus nerve respectively. The glomus vagale characteristically displaces the internal carotid artery anteriorly or medially and the jugular vein posteriorly. Paragangliomas may be familial and in such cases may be multiple and may very rarely show malignant transformation. On US paragangliomas do not appear particularly vascular despite showing avid enhancement on contrast-enhanced CT and MRI. They may show a characteristic 'salt and pepper' appearance on MRI (**Figure 37.43**) with the 'pepper' or low-signal appearance representing flow voids of feeding vessels.

Tuberculosis

Tuberculosis is commonly seen in the cervical lymph nodes but may occasionally be seen in the larynx or pharynx. The posterior triangle and supraclavicular nodes are frequently affected. In the early stage nodes may simply be enlarged and show homogenous enhancement on CT or MRI but later the nodes adopt the classical matted appearance with central necrosis (**Figure 37.44**).[183]

Atypical mycobacterial cervical adenitis is a cause of a unilateral persistent neck lump in a child under 5-years of age, often associated with an overlying violaceous skin appearance. US (**Figure 37.45**) reveals a marked decrease of echogenicity in the early stages and intranodal liquefaction with sinus tracts in the advanced stages.





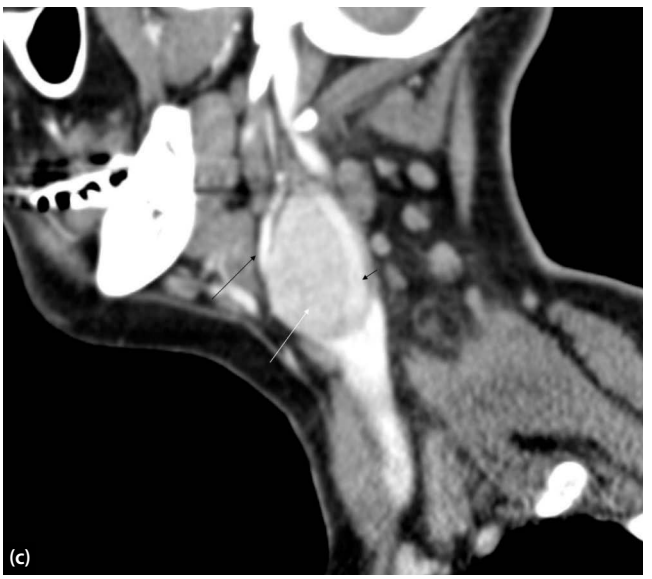


Figure 37.42 US **(a)**, axial **(b)** and sagittal reformatted **(c)** contrast-enhanced CT showing a level 2 mass (white arrows) lying between splayed internal (ICA, short black arrows) and external carotid arteries (ECA, long black arrows) consistent with a carotid body tumour. Note the carotid body tumour is avidly enhancing on contrast-enhanced CT but relatively avascular on US.

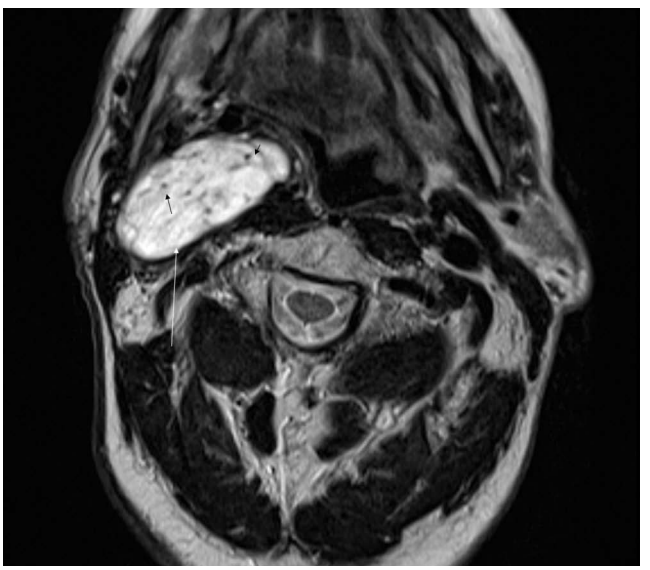


Figure 37.43 Axial T2-weighted MRI showing a high signal right carotid space mass (white arrow) containing several signal voids (small black arrows) consistent with a paraganglioma.

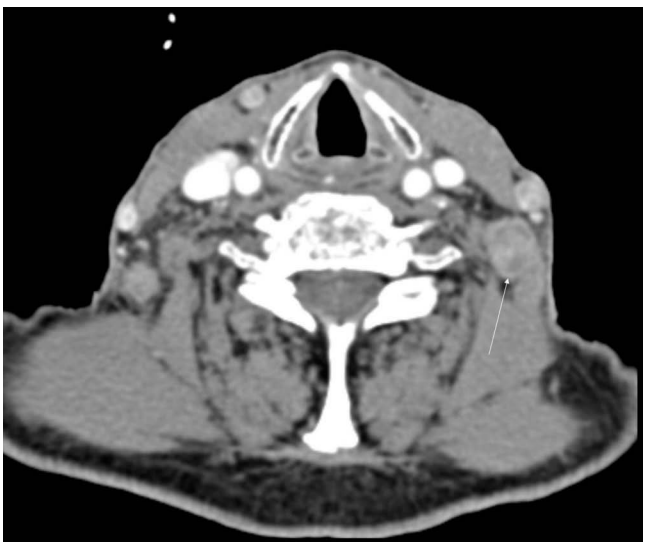


Figure 37.44 Axial contrast-enhanced CT showing tuberculous partly necrotic nodes in the left lower neck (white arrow).

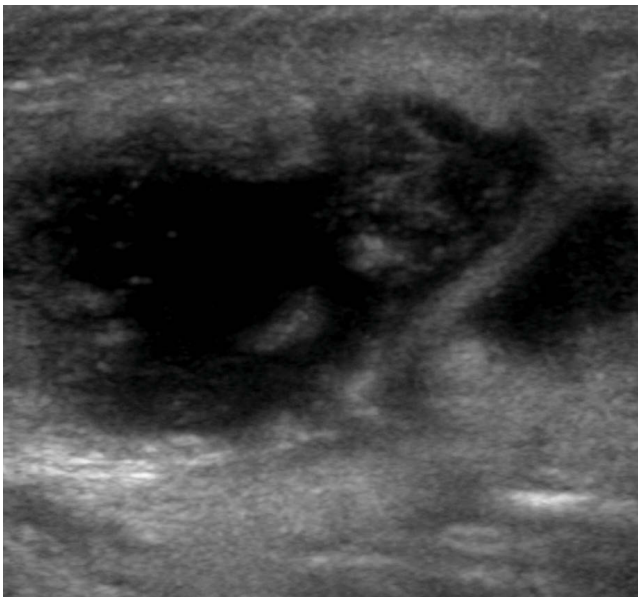


Figure 37.45 US of a child showing an irregular septated mass overlying which clinically was skin violaceous discoloration consistent with mycobacterial cervical adenitis.

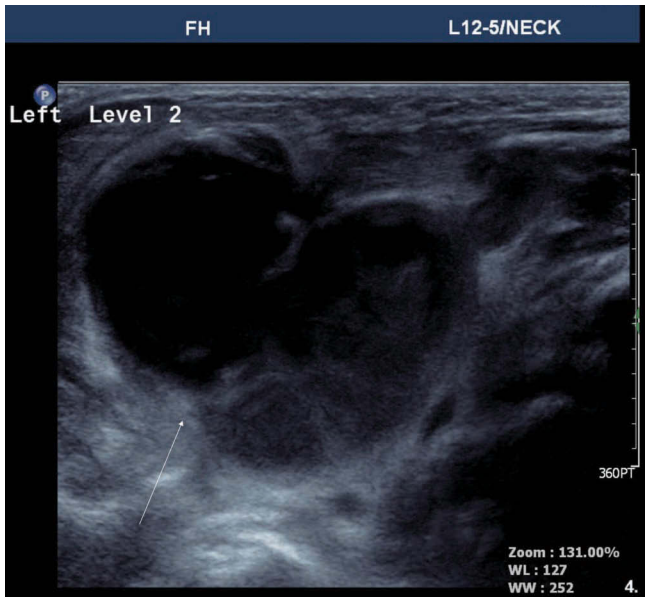


Figure 37.46 US in a child, presenting with neck swelling and fever, showing a suppurative node (white arrow).

THE HOT NECK

Patients presenting with fever, pain, swelling, odynophagia, sore throat or trismus have to be considered to have neck sepsis and require imaging to assess whether surgical intervention is required (**Table 37.1**). The commonest sources are tonsillar or odontogenic infection. US should be the first-line investigation in children (**Figure 37.46**) and any superficial infection but contrast-enhanced CT of the neck and mediastinum is the imaging modality of choice to assess the extent of infection and any complications such as airway compromise, vascular thrombosis, neural dysfunction and ultimately necrotizing mediastinitis.[184–187] These complications may be life-threatening and surgery remains the mainstay of treatment but conservative medical treatment is effective in selected cases.[188] The patient's condition usually precludes the use of MRI but is extremely useful if a discitis and prevertebral abscess are suspected.

US is a very reliable diagnostic tool in the diagnosis of pus collections in the neck with a sensitivity of 96% and specificity of 82% and can show small collections to resolve without surgical drainage.[189] However should a parapharyngeal or peritonsillar abscess be suspected clinically, then CT rather than US should be performed.[190, 191] Meyer et al.[192] argue that as duration of localized symptoms of deep neck infection in children does not predict findings of abscess on CT, it is appropriate to obtain a CT scan upon presentation in all children with concerning symptoms for neck abscess. The findings on CT may include inflammatory stranding and loss of fat planes in cases of cellulitis, enhancing inflammatory phlegmon and abscess formation, characterized by a focal low-attenuation area with a surrounding enhancing rim (**Figure 37.47**). However, occasionally fluid collections without wall enhancement have yielded pus on surgical exploration.[193]

TABLE 37.1 Imaging in the Hot Neck, what the surgeon needs to know

Is there an abscess or just inflammatory change?
If an abscess is present, in which space/spaces?
How large is the abscess?
Extent of abscess
Is the mediastinum involved?
Is the airway compromised?
Is there jugular vein thrombosis?

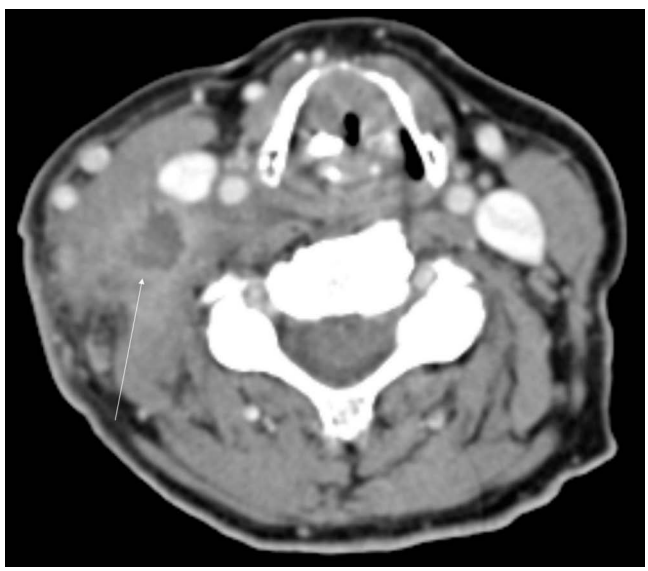


Figure 37.47 Axial contrast-enhanced CT showing a low-attenuation area with surrounding enhancing rim (white arrow) and surrounding inflammatory change consistent with an abscess in the lower neck.

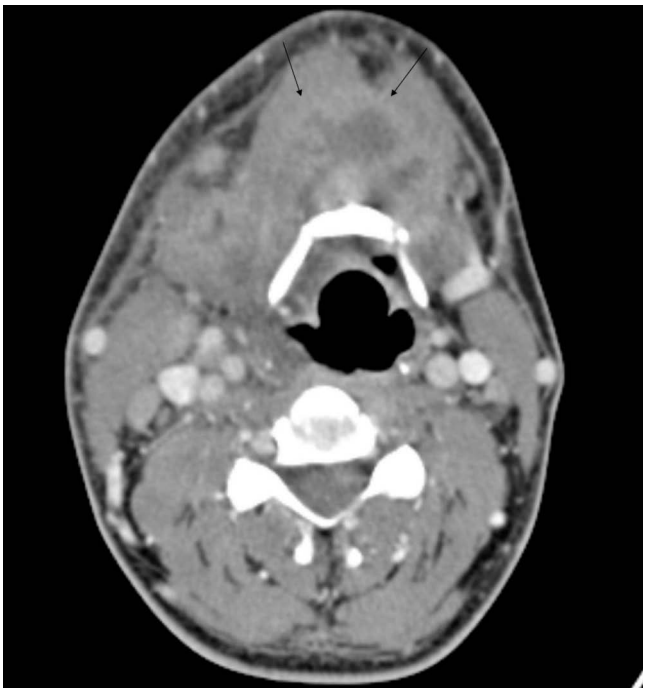


Figure 37.48 Axial contrast-enhanced CT showing an ill-defined phlegmon/abscess (black arrows) in the floor of mouth with an odontogenic source identified in the mandible.

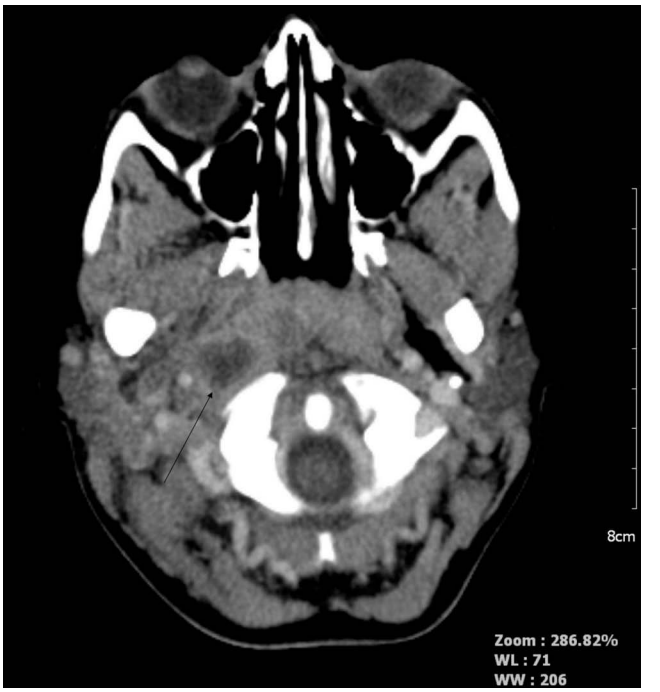


Figure 37.49 Axial contrast-enhanced CT in a child showing an abscess within a retropharyngeal node (black arrow).

Contrast-enhanced CT has a positive predictive value of 79.6–82% for diagnosing deep neck abscesses, increasing to 91.3% when more than one deep neck space is involved but decreasing to 50% in patients with isolated retropharyngeal abscess.[194, 195]

Infections in the sublingual, submandibular and masticator spaces are often odontogenic in origin and these patients should also have an orthopantomogram (OPG) to assess the dentition.[196] Infection originating in the incisors to premolars mandibular teeth usually spread to the sublingual space while infection of the molars spread to the submandibular space (**Figure 37.48**).

Retropharyngeal space infection occurs mainly in children due to suppuration of a retropharyngeal node (**Figure 37.49**) and is usually due to naso- or oropharyngeal infection. Infection from here may track into the posterior mediastinum above the level of the carina.

Tonsillitis is the commonest infection to occur in the pharyngeal mucosal space and usually responds to antibiotics but occasionally patients may develop tonsillar or peritonsillar (quinsy) abscesses that then involve the parapharyngeal and retropharyngeal spaces (**Figure 37.50**).

Cervical lymphadenitis is common in children and refers to inflamed, enlarged and tender cervical lymph nodes, usually due to an upper respiratory tract illness.

It is important to realize that head and neck cancers can present as infection in patients over 40 years with one study quoting a prevalence of 4.9%.[197, 198] In such patients any neck mass that fails to resolve after a course of antibiotics should be further investigated by FNA, endoscopy and cross-sectional imaging.

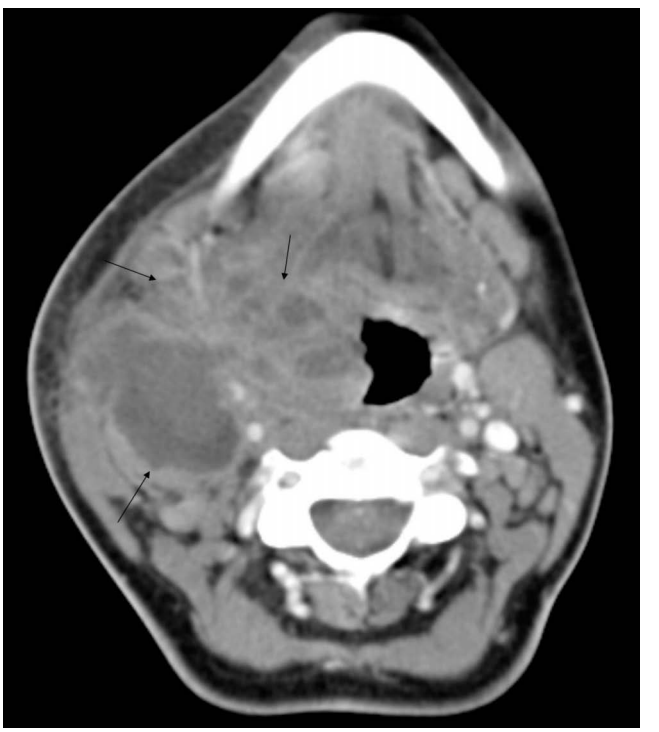


Figure 37.50 Axial contrast-enhanced CT showing a multiseptated abscess (black arrows) occupying multiple spaces arising from untreated tonsillitis.

KEY POINTS

- Imaging of the neck is integral to diagnosis, treatment and follow-up of neck lumps.
- The choice of imaging modalities depends on the clinical scenario and the working diagnosis.
- Dedicated head and neck radiologists can provide invaluable help in diagnosis, especially in complex cases.
- Cross-sectional imaging is mandatory in almost all cases of head and neck cancer.
- Based on the clinical picture, complementary information can be obtained from a combination of imaging modalities.
- All imaging is best done before any surgical intervention to avoid artifacts caused by the surgery.

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CHAPTER 38

NECK TRAUMA

Andrew J. Nicol and Johannes J. Fagan

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SEARCH STRATEGY

Data in this chapter may be supported by a Medline search using the following keywords: trauma, cervical, trachea, esophagus, and vascular.

INTRODUCTION

The issue dominating discussion on the management of penetrating neck trauma for the past few decades is whether penetrating neck injuries require mandatory exploration. There has been a distinctive paradigm shift from mandatory exploration towards more selective, conservative management based on clinical evaluation and specialized investigations. Introduction of diagnostic tools such as flexible endoscopy, oesophagography, high-resolution computed tomography (CT), and duplex doppler have improved non-operative evaluation of aerodigestive and vascular injuries. The realization that certain injuries may be treated non-operatively and the management of selected arterial injuries by endovascular techniques have further promoted the concept of selective exploration of the neck.

THE TRAUMA PATIENT: GENERAL PRINCIPLES

Primary survey (survival assessment)

Resuscitation should be performed in accordance with the Advanced Trauma Life Support (ATLS®) principles.[1] The Primary Survey is an initial assessment of factors that cause early deaths in trauma patients. It focuses on factors such as hypoxia, hypovolaemia, tension pneumothorax and head injury.

AIRWAY AND CERVICAL SPINE PROTECTION

The patient is examined for evidence of airway obstruction; this may present as stridor and use of accessory muscles of respiration. The neck should be stabilized with a cervical collar or sandbags until cervical spine injury is excluded. Major facial fractures, in particular mandibular fractures, and large cervical haematomas may compromise the airway. Patients with transcervical gunshot wounds (GSWs) may not have airway problems initially, but must be closely observed as they can rapidly develop airway obstruction. A chin lift and jaw thrust procedure should be done to try to overcome the obstruction. Patients with Glasgow coma scores (GCS) of ≤8 usually require intubation to protect the airway. An endotracheal tube may sometimes be inserted directly into the trachea through a penetrating cervical injury. Cricothyroidotomy must be considered if intubation fails. It should subsequently be converted to a formal tracheostomy within 24 hours, as the small tube is difficult to keep clean, and to prevent subglottic stenosis.

BREATHING

The chest should be examined for chest wall movement and air entry. Tension pneumothorax and haemothorax

are life-threatening conditions; immediate intervention based on clinical diagnosis is mandated before X-rays are obtained. Tension pneumothorax presents with hypoxia, restlessness, hyper-resonance to percussion, decreased air entry, contralateral tracheal shift, and elevated jugular venous pressure. It is decompressed by needle thoracocentesis; a large bore needle is initially inserted through the 2nd intercostal space in the mid-clavicular line, followed by insertion of a chest drain. A large haemothorax is identified by dullness to percussion and decreased air entry, and is also managed with an intercostal drain.

CIRCULATION AND PERFUSION

In the shocked patient, insert two high-flow lines with 14-gauge cannulae in the antecubital fossae. The line should not be inserted on the same side as a vascular injury with massive bleeding, for if there is a venous injury, intravenous fluids will merely bleed out. In the shocked patient, start with two litres of crystalloid; if the blood pressure does not improve, proceed to a transfusion of 0-negative blood, and arrange blood cross-matching. A shocked patient with warm peripheries may have neurogenic shock secondary to spinal cord injury. This would result in low blood pressure and bradycardia, potentially masking a significant vascular injury. Active bleeding from a cervical wound may be controlled with a compressive dressing or digital pressure. Failing this, a large Foley's catheter may be inserted into the wound, the bulb inflated, and the catheter cross-clamped to stop blood pouring through the catheter. This can be a very effective form of haemostasis particularly with bleeding from the subclavian and cervical vessels.[2] Throughout, the patient should remain recumbent, or the neck wound must be covered with an occlusive dressing when the patient sits up, to prevent air embolism.

DISABILITY

The GCS and pupil size and reactivity to light are recorded, and power in the limbs is assessed.

EXPOSURE

All clothing is removed in order to avoid missing associated injuries. The patient is kept warm.

Adjuncts to primary survey

Adequate monitoring, including ECG, pulse oximetry and non-invasive blood pressure monitoring is instituted. A rectal examination to exclude a urethral injury should be performed prior to inserting a urinary catheter. The haemoglobin level, blood glucose and arterial blood gas are checked. Imaging is essential. In a well-resourced trauma centre, this would include cross-sectional CT or MR imaging. Alternatively, cervical spine chest and pelvic X-rays are essential. In a patient with isolated penetrating neck trauma, a chest X-ray and cervical spine X-rays will suffice. Exclude a haemo- or pneumothorax, pneumomediastinum (tracheal or oesophageal injury), and widened mediastinum on chest X-ray. The mediastinal width on a supine chest X-ray should not exceed 8 cm; a widened mediastinum is suggestive of major intra-thoracic injury and must be further investigated with CT angiography. Cervical spine X-ray is used to exclude spinal column injury and prevertebral air (pharyngeal or oesophageal injury). Non-urgent X-rays should be requested only on completion of the secondary survey.

Secondary survey

A detailed head-to-foot examination of the patient is conducted. In firearm injuries, the location of the wounds must be noted and the direction of the tract established so as to determine which anatomical structures may have been injured. X-rays (AP and lateral) are obtained in the absence of an exit wound to locate and determine the tract of the bullet. If the patient has not been intubated, examine the cranial nerves and exclude Horner syndrome. Note the presence of a large cervical haematoma, subcutaneous emphysema, the jugular venous pressure and tenderness over the mandible. If a nasogastric tube has been inserted, the presence of blood in the nasogastric tube should be looked for.

KEY POINTS

- Wounds should not be probed as this may cause massive bleeding from an arterial injury.

Check the peripheral pulses for discrepancy or absence. Examine the distal carotid and superficial temporal artery pulses, and listen for bruits. Again exclude a haemo/pneumothorax and listen to the heart sounds. The abdomen and pelvis should be examined, followed by a full neurological examination during which spinal cord and brachial plexus trauma are excluded. Note the presence of hemiplegia or Brown-Sequard syndrome (hemitransection of spinal cord). The patient should be logrolled in order that the back can be examined for trauma.

History

Take a history with specific reference to the nature of the trauma. Enquire about symptoms pointing to oesophageal injury (haemoptysis, haematemesis, dysphagia, and odynophagia), and recurrent laryngeal nerve or laryngeal injury (dysphonia, stridor). Past medical and surgical history is documented, as well as the time of the patient's last meal.

Further investigations

Any further X-rays that are required after the secondary survey are now completed. Special investigations such as CT scan, ultrasound and gastrografin or barium studies may now be requested in a haemodynamically stable patient.

Full documentation

All injuries are documented and the patient is referred for definitive care.

AETIOLOGICAL CLASSIFICATION

- Penetrating
  - stabs
  - GSW
    - low kinetic energy
    - high kinetic energy
    - shotgun
- blast
- blunt.

Unlike stab wounds and low kinetic energy GSWs, close-range shotgun, rifle, and bomb injuries cause extensive soft tissue trauma.

ZONES OF THE NECK

The neck contains three principal anatomic components i.e. vascular (carotid, vertebral, and subclavian arteries; jugular and subclavian veins), digestive (pharynx and oesophagus) and respiratory (larynx and trachea). Roon & Christensen's classification into three zones is most commonly used for description of the site of cervical trauma (**Figure 38.1**).[3] All three zones contain major vascular, and aerodigestive structures. However injuries to zones I and III are both diagnostically and surgically more challenging.

- Zone I: Sternal notch / clavicle to cricoid cartilage
- Zone II: Cricoid cartilage to angle of mandible
- Zone III: Angle of mandible to base of skull

In a second classification system by *Monson*, the transition between zones I and II is at the sternal notch.[4] Both retrospective and prospective studies and review articles of penetrating cervical trauma fail to take into account these differences in the classification systems used.[4] Although transcervical injuries (injuries that cross the mid-line of the neck) are associated with vascular or aerodigestive injuries in 73–100% of patients, neither classification system takes cognisance of transcervical injuries.

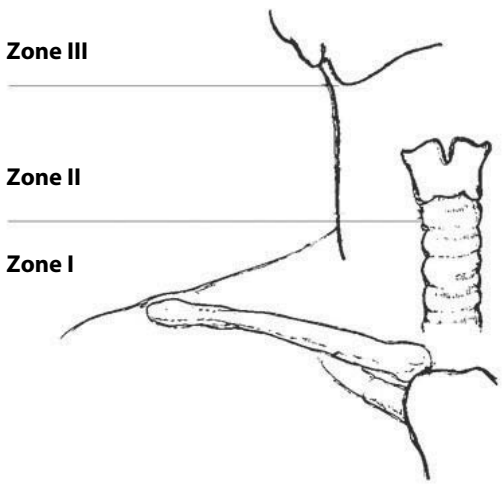

Figure 38.1 Zones I – III: Roon and Christensen classification.

MANDATORY VERSUS SELECTIVE EXPLORATION OF PENETRATING CERVICAL INJURIES

Prior to World War II, non-operative treatment of penetrating neck injuries was associated with a mortality of 15–18%.[5] Following experience in World War II, Bailey in 1944 proposed early exploration of penetrating neck injuries. Coupled with the introduction of antibiotics and tracheostomy, early exploration reduced the mortality rate to 7%.[6] In 1956, Fogelman and Stewart reported that mortality for patients not immediately explored was 35% vs. 6% for those that had been promptly explored. They concluded that all penetrating neck wounds that violated the platysma required surgical exploration.[7] Mandatory exploration of the neck whenever the platysma muscle had been breached subsequently became common practice. In 1963 Stone questioned the need for mandatory exploration for civilian injuries.[8] Ever since that time controversy has reigned about the relative merits of mandatory exploration vs selective exploration for low-velocity gunshot and sharp penetrating cervical wounds. The majority of trauma centres currently advocate some form of selective conservative management.[9]

Mandatory exploration

Proponents of mandatory exploration of stable patients with low-velocity GSWs and stab wounds that breach the platysma muscle consider that the risk of missing an unsuspected vascular or aerodigestive tract injury outweighs the morbidity and expense of negative exploration. They point to the unreliability of clinical evaluation, that diagnostic studies do not have 100% sensitivity to detect oesophageal and vascular injuries, low morbidity associated with negative exploration, additional time and effort associated with expectant observation, and the significant morbidity and mortality associated with delayed detection and repair of oesophageal injury. Yet, vascular and oesophageal injuries can be missed when the neck is explored without the assistance of pre-operative angiography, oesophagography and/or oesophagoscopy.

Selective exploration

Protagonists of selective exploration quote the high rate (36–89%) of negative mandatory exploration,[9–11] good sensitivity and specificity of special investigations such as angiography, doppler, barium swallow, rigid oesophagoscopy, and flexible laryngotracheobronchoscopy; expense of prolonged hospitalization following negative exploration; the fact that many injuries (e.g. thyroid, pharyngeal and certain venous injuries) that are detected at mandatory exploration may be treated conservatively; and that neck exploration leaves an unsightly scar (**Figure 38.2**).

TABLE 38.1 Selective conservative management of penetrating cervical injuries

Series	No of patients	Explored	Endovascular management	Negative explorations	Observed	Mortality
Narrod[12]	77	62 %	NR	15%	29%	0%
Campbell[13]	108	24%	NR	0%	82%	1.2%
Ngakane[14]	109	NR	NR	NR	97%	1.8%
Demetriades[9]	335	20%	NR	15%	80%	0%
Thoma[15]	203	12%	4%	0%	78%	0%
Van Waes[16]	77	8%	1%	0%	90%	0%

NR = not reported.

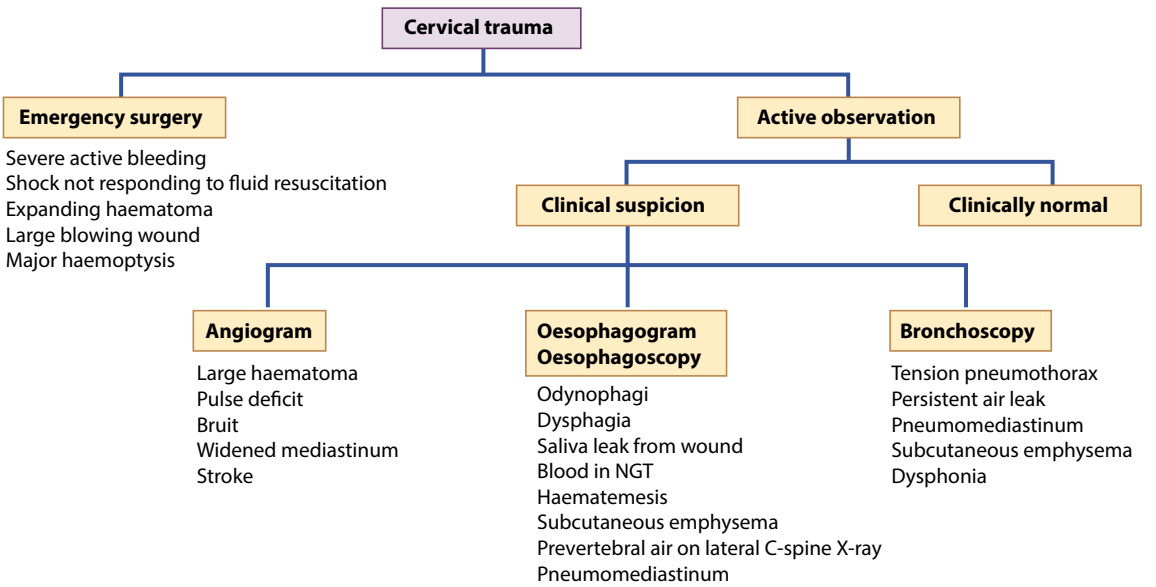

Figure 38.2 Selective surgical exploration algorithm.

Negative exploration in centres practising selective exploration ranges between 9% and 62%.[10–12] The safety of selective conservative management of penetrating cervical injury is apparent from the results of six prospective studies summarized in **Table 38.1**. Mortality in the studies by Campbell[13] and Ngakane[14] was not attributable to cervical injury, but to associated trauma. Two recent prospective studies from our institution have validated the fact that selective non-operative management of penetrating neck injuries is effective and safe.[15, 16]

KEY POINTS

- Indications for emergency surgery with such a selective approach include severe active bleeding, hypovolaemic shock not responding to resuscitation, a rapidly expanding haematoma, a large blowing wound and major haemoptysis.

The remaining patients are assessed clinically and appropriate radiological and endoscopic investigations are done only if there is a suspicion of visceral injury.

While the importance of early diagnosis of occult vascular injury is debatable, delayed diagnosis of oesophageal perforation is accompanied by increased morbidity and mortality.[17, 18] Because of concerns about reliability of physical assessment alone, some protagonists of selective exploration therefore advocate mandatory oesophageal and vascular studies; others have employed active observation with special investigations only if the clinical examination is equivocal.

Active observation with selective special investigations

Demetriades et al. reported in a prospective study of 335 penetrating neck injuries that a combination of clinical and selective investigations yielded a specificity of 85%, and sensitivity of 100% to identify clinically significant vascular and aerodigestive tract injuries. Only 38% of patients with surgical emphysema required exploration. They concluded that selected exploration can be based on careful initial and repeated clinical examinations.[9] They advocate emergency exploration for the absolute indications for neck exploration noted previously. They do not consider soft signs such as shock responding to resuscitation, minor active bleeding, haematoma, dyspnoea,

subcutaneous emphysema, hoarseness, dysphagia or minor haematemesis to be absolute indications for exploration; such patients are assessed individually, taking into account the direction of the injury tract, and the severity of the clinical signs. If the tract courses away from larynx, trachea, oesophagus and carotid sheath, then no further investigations are done. If the tract is directed towards the midline, then contrast oesophagography, and/or endoscopy are done. Chest X-ray is requested if chest pathology is suspected. Hall et al. support this approach in a report on the safety of active observation of children with penetrating injuries in Zone II.[5] Although transcervical gunshots are twice as likely to have visceral/vascular injury as gunshots that do not cross the midline (79% vs. 31%, $p = 0.02$), 80% may be safely managed non-operatively by active observation and selective special investigations.[19]

Spiral CT scanning to evaluate the neck shows promise.[20] When CT scan in the stable patient reveals that the trajectory courses away from vital structures, then employment of invasive studies appears to be superfluous.

SPECIFIC INJURIES

Pharyngeal injury

Hypopharyngeal injury should be suspected in Zone II penetrating injuries, particularly in the presence of dysphagia, odynophagia, voice change, haemoptysis, haematemesis, and surgical emphysema. Flexible nasopharyngoscopy may reveal oedema, blood in the pharynx, or the perforation may be visible if located in the superior hypopharynx. Direct pharyngoscopy should reveal all injuries, but oesophagography is unreliable.[21] In a retrospective study of 47 hypopharyngeal injuries, Stanley et al. reported no complications in supra-arytenoid hypopharyngeal injuries, as opposed to a 22% complication rate for infra-arytenoid hypopharyngeal injuries. They conclude that upper hypopharyngeal injuries may be managed non-operatively; this part of the hypopharynx is capacious, has a low-intraluminal pressure and is enveloped by both the middle and inferior constrictor muscles. The lower hypopharyngeal funnels into the cricopharyngeus segment and is less capacious, has higher intraluminal pressure and is surrounded only by the inferior constrictor muscle; it should explored, repaired and drained like oesophageal injuries.[22]

Oesophageal injury

Early recognition and treatment of oesophageal perforation is the key to favourable outcome. Missed oesophageal injury has high morbidity and mortality. Intervention delays of >12 hours for iatrogenic oesophageal injury has a mortality rate of 40% as opposed to 9% if <12 hours.[17] In a retrospective multicentre study, Asensio et al. compared the outcome of patients that underwent diagnostic studies, with patients taken straight to the operating room. The study revealed a significantly increased oesophageal complication rate (41% vs. 19%), and length of ICU stay with patients having diagnostic studies. They concluded that time delays in instituting active management incurred by investigations associated with selective exploration can lead to increased morbidity and mortality.[18] This report does not however distinguish between the cervical and thoracic oesophagus. Whether their conclusion applies to isolated cervical oesophageal injury is therefore open to question, particularly in view of reports of successful outcome of small cervical oesophageal injuries treated conservatively. However, centres practising selective management of penetrating neck injuries should make rapid diagnosis and definitive repair a priority.

ACCURACY OF DIAGNOSIS OF OESOPHAGEAL INJURY

Dysphagia, haematemesis and odynophagia are symptomatic of penetrating oesophageal injury. Clinical evidence includes surgical emphysema and a salivary leak. X-ray may reveal retropharyngeal air, retropharyngeal oedema, haematoma, tracheal deviation, and a pneumomediastinum. Clinical evaluation has a sensitivity of 80% (50% for stabs, 100% for GSWs), a specificity of 64%, and an accuracy 72%.[17] Sensitivity of barium swallow is 48–100%, and of oesophagoscopy 40–90%.[23, 24] In a prospective study, Weigelt et al. reported 89% sensitivity, 100% specificity and 94% accuracy (AP and lateral views with cineradiography) for barium swallow; flexible oesophagoscopy was unreliable, particularly in the proximal oesophagus as the mucosa cannot be effaced as with rigid oesophagoscopy; rigid oesophagoscopy had a sensitivity of 89%, specificity of 95% and accuracy of 94%; and a combination of oesophagography and oesophagoscopy had a sensitivity of 100%.[17] Wood et al. reported sensitivity of oesophagography of 100% and specificity of 96%, and cautioned that oesophageal and vascular injury can be missed at neck exploration.[25] Flowers et al. and Srinivasan et al. have however more recently reported sensitivities of 100%, and specificities of 96% and 92.4% respectively, for flexible oesophagoscopy to detect the presence of penetrating injury of the oesophagus.[26, 27] Because barium, if aspirated, may induce serious pulmonary problems, it should not be used in trauma patients and an appropriate water-soluble contrast agent (e.g. gastrografin) should be used.

DO ALL OESOPHAGEAL INJURIES NEED TO BE EXPLORED?

Treatment of oesophageal injury varies from observation, to simple repair of the wall +/- drainage of deep neck spaces, to primary diversion of salivary flow to the skin by means of partial or total exteriorization procedures. All high-kinetic injuries should be explored. The management of stab wounds and low-kinetic energy GSWs is more contentious. Wound site, size, mechanism of injury, time delay, associated injuries, availability of and expertise with diagnostic tests such as oesophagography and oesophagoscopy, and availability of theatre time all play a role in determining the management of oesophageal injury. Generally it is recommended that, should barium swallow be positive or equivocal, one should proceed to rigid oesophagoscopy; if positive, then the oesophagus is explored. However, Ngakane et al. concluded from a prospective study of penetrating visceral

injuries of the neck, that should oesophagography reveal minimal leakage of contrast, then patients can be managed conservatively; oesophagography is repeated on day 5, prior to commencing oral feeding.[14] Similarly favourable outcomes of small cervical oesophageal perforations treated conservatively been reported by Mandal et al. and others.[28]

SURGICAL TECHNIQUE

The majority of oesophageal injuries can be repaired primarily. The remainder are repaired by resection and anastomosis, or are simply drained. Intravenous antibiotics and enteral or parenteral nutrition should be instituted. Adequate drainage, suction or dependent, is important as even with a technically sound repair, 13% develop fistulae.[11] If part of the oesophagus has been blown away, if mediastinitis or sepsis is already present, or if oesophageal injury extends into the chest, then a lateral cervical oesophagostomy may be required. There is no evidence to favour a double- or single-layered repair. Local infrahyoid strap or sternocleidomastoid muscle flaps can be used to buttress the repair, or used as an interposition between an oesophageal injury and a vascular or tracheal repair.[29] Barium swallow is done on day 5–7, as 50% of post-operative oesophageal fistulae are asymptomatic and detected only on contrast study.[11] Should a fistula or sinus be present, the drain is retained.

COMPLICATIONS OF OESOPHAGEAL INJURY

Oesophagocutaneous fistulae occur in 9–28% of oesophageal injuries.[29] They occur more commonly with GSWs, but generally close spontaneously. Oesophagotracheal fistulae are repaired with interposition of a muscle flap. More serious complications include abscess formation, mediastinitis, septicaemia and death.

Tracheal injury

Cervical tracheal injury is relatively uncommon, and frequently associated with oesophageal, vascular or spinal injury. Symptoms of tracheal injury include a blowing wound, surgical emphysema, haemoptysis and hoarseness. Chest X-ray may reveal surgical emphysema and pneumomediastinum. The priority is to secure an airway. The trachea can sometimes be intubated through a blowing wound in the neck. Tracheotomy is appropriate in the presence of laryngeal trauma to avoid further injury to the endolarynx, when it is not possible to safely pass an endotracheal tube, or with quadriplegia requiring ventilatory support. Former teaching that nasotracheal or orotracheal intubation should be avoided as it may aggravate an existing tracheal injury or cause a false passage appears to have been overly cautious.[30] Distal tracheobronchial disruptions can be bypassed under direct vision with an introducer passed through a rigid bronchoscope, or by intubating over a flexible bronchoscope. Tracheobronchoscopy can be useful to assess the injury, but the diagnosis is usually readily apparent on exploring the neck for associated injuries. Minor tracheal injuries in patients not otherwise requiring cervical exploration can be managed expectantly. In cases of marked surgical emphysema, a tracheotomy might expedite recovery. Tracheal repair is effected with interrupted sutures. When there is an associated oesophageal or vascular injury, then the repair can be bolstered with a local muscle flap. In selected cases a tracheotomy or an endotracheal tube may be used to protect the tracheal repair.

Vascular injury

The common carotid artery is the most frequently injured major vessel; it accounts for 22% of vascular injuries.[31] Current debate centres on evaluation of the asymptomatic patient, and optimal treatment of vascular trauma. The majority of published series are small, retrospective, and from single centres.

CLINICAL EVALUATION

Hard clinical signs of vascular injury are expanding haematoma, external haemorrhage, absent or diminished distal pulses, ischaemic neurological deficits, or coma. The reported accuracy of clinical evaluation varies widely. Scalafani et al. reported a specificity of 80% and sensitivity of 61%; Meyer et al. reported an accuracy of 68%.[32] Demetriades et al. reported a sensitivity of 100% for clinical detection of significant vascular injury.[33] The widely disparate results may reflect shortcomings of retrospective data collection, and a lack of emphasis placed on clinical decision-making in centres with a bias towards routine angiography or exploration.

INVESTIGATIONS

The gold standard investigation remains 4-vessel arch angiography with selective catheterization. Angiography has the following benefits: identifies the site of injury; identifies subclinical vascular injury including vertebral artery trauma; serves as a roadmap for the surgeon; delineates the extent of crossover circulation through the Circle of Willis; and identifies injuries amenable to endovascular intervention. However, helical CT angiography is largely replacing conventional angiography and has a 90–100% sensitivity and specificity to detect arterial injury.[20] Vascular injuries in Zone II are readily exposed, and with Zone II penetrating injuries, the chance of detecting an asymptomatic arterial injury by angiography is less than 1%, which approaches the complication rate of angiography.[4] With penetrating injuries in Zone II, angiography may therefore be employed selectively for patients with clinical suspicion of a vascular injury, or when the tract of a GSW passes close to vascular structures. Vascular injuries in Zones I and III can however be difficult to assess clinically, and surgical exposure and vascular control are more challenging. Hence pre-operative angiography of suspected vascular injuries in Zones I and III is generally recommended. Demetriades et al. reported that colour-flow duplex Doppler (CFD) imaging, when combined with clinical examination, had a sensitivity of 91% and specificity of 99% to detect vascular injury. CFD only missed an intimal tear which did not require treatment.[33] CFD however requires trained personnel; is not always readily available; is best avoided if there is a suspected cervical column

injury; it may not demonstrate very well the origins of cervical arteries from the aortic arch, the arteries close to the skull base, and the vertebral arteries; and it is difficult to identify individual branches of the external carotid artery.

CAROTID REVASCULARIZATION VERSUS LIGATION

With the introduction of vascular surgical techniques during the Korean War, primary repair of carotid artery injuries was recommended. In 1973 Bradley concluded from two autopsy studies that revealed haemorrhagic brain infarction, that revascularization should not be attempted in patients with severe neurological deficits.[34] Fear about converting an ischaemic into a haemorrhagic infarct by reperfusion and hence worsening the neurological outcome has since been a major concern to vascular surgeons, and has fuelled the dilemma of ligation vs. reperfusion. In 1978 Liekwig and Greenfield showed that patients with severe neurological deficits just short of coma had significantly better results with reperfusion.[35] This was supported by Brown et al. in 1982 who showed that revascularization in patients with pre-operative coma (lack of meaningful response to verbal or noxious stimuli) was indicated when ischaemia had only been present for a short period of time prior to surgery (**Figure 38.3**).[36]

PSEUDOANEURYSMS AND INTIMAL INJURY

Clearly the risk of surgery for pseudoaneurysms (focal, eccentric widening of the lumen extending beyond the arterial wall), intimal defects and intimal flaps, should not exceed the risk of complications developing from the arterial pathology. Pseudoaneurysms, intimal defects and intimal flaps have been managed conservatively.[37, 38] However, studies are small and the safety of a conservative approach particularly with respect to the carotid artery has not been confirmed. Patients managed conservatively should be followed with arteriography to confirm that the lesion does not increase in size.

VERTEBRAL ARTERY INJURY

With the increased availability of angiography, vertebral artery injury is being more frequently recognized.[39] Patients may present with acute bleeding or with late complications of thrombosis, false aneurysms, bleeding, arteriovenous fistulae and stroke. Torrential bleeding may be encountered from a lacerated vertebral artery. Arteriovenous fistulae may present with a bruit, thrill, haematoma, neurological deficits, or cardiac failure. A neurological deficit seldom occurs in the presence of a normal contralateral vertebral artery and intact collateral circulation.[40] Mortality from isolated vertebral artery trauma ranges from 5% to 17% but increases to 50% if there is an associated injury of the carotid artery.[41] The majority of vertebral artery injuries can be managed by angiographic embolization. If the injury is discovered at emergency surgery, the vessel should be ligated. This is fairly simple if the injury is located at a point before the vertebral artery enters the foramen transversarium at the level of the 6th cervical vertebra. Once inside the vertebral canal, ligation may be achieved with ligaclips. Alternately, bone wax should be used to tamponade bleeding, followed by angiographic embolization.

ENDOVASCULAR TECHNIQUES

Endovascular techniques are playing an increasing role in the treatment of both acute and late manifestations of vascular trauma, particularly at the skull base. False aneurysms and arteriovenous fistulae can be treated with covered stents, or by trapping the lesion proximally and distally with balloons or coils, once good cross-flow across the Circle of Willis has been demonstrated (**Figures 38.4** and **38.5**).

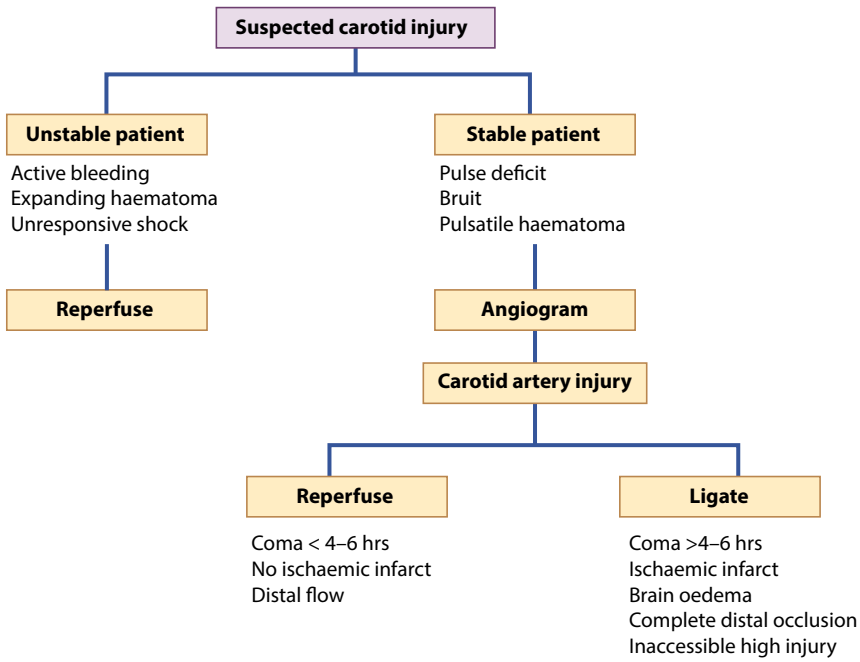

Figure 38.3 Recommended protocol for carotid ligation vs. reperfusion.

Bleeding from branches of the external carotid artery can be controlled by embolization.

VENOUS INJURY

The external jugular vein may be ligated if injured. The internal jugular vein may be repaired by lateral venorrhaphy, or ligated. Should both internal jugular veins have been injured, then at least one vein should be repaired to prevent facial swelling, and sequelae of raised intracranial pressure such as blindness, SIADH and even death. A remnant of the contralateral internal jugular vein or saphenous vein can be used should a graft be required.

Chylous injury

Patients with Zone I injuries rarely develop a chylothorax due to injury to the thoracic duct or right lymphatic duct. Although one can attempt a diet of medium-chain triglycerides, Worthington et al. reported that conservative treatment is uniformly unsuccessful, and advocate early ligation via thoracotomy.[42]

Neurological injury

Significant brachial plexus nerve injury should be repaired within 24–72 hrs.

EXPLORATION OF THE NECK: GENERAL PRINCIPLES

- IVI lines, suction, blood in theatre
- General anaesthesia: crash induction with cricoid pressure
- Airway:
  - nasotracheal/orotracheal intubation
  - cricothyroidotomy or tracheotomy
- Position:
  - supine
  - neck extended, turned to opposite side, if no C-spine injury
- Exposure:
  - chest and face for Zones I and III injuries, to permit additional surgical exposure if required
  - contralateral groin and lower leg to permit harvesting of saphenous vein for grafting
- Approach:
  - localized injury: horizontal skin crease incision, subplatymal flaps
  - wider exploration: long incision along anterior border of sternocleidomastoid muscle
- Additional exposure:
  - Zone I: divide omohyoid muscle; bilateral exploration: apron flap
  - Zone III: anterior dislocation of the mandible.

SUMMARY

Management of penetrating injuries of the neck remains controversial. Reasons for the controversy include paucity of well-designed, large, prospective studies; the uncommon occurrence of oesophageal injury; the variable levels of radiological and surgical expertise at trauma centres confronted with cervical injuries; the wide spectrum of the site and severity of injuries and of aetiological agents, as well as the lack of a uniform classification system when reporting neck injuries.

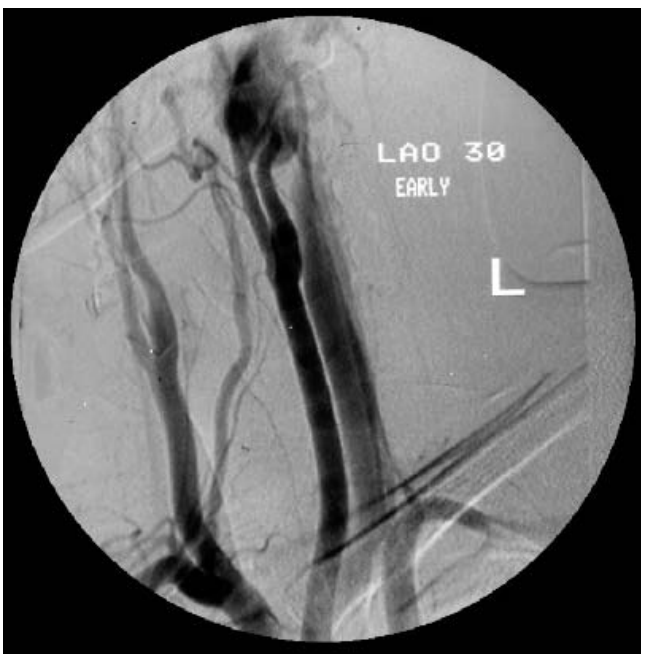

Figure 38.4 False aneurysm of internal carotid artery, with carotico-jugular fistula following stab wound at base of skull.

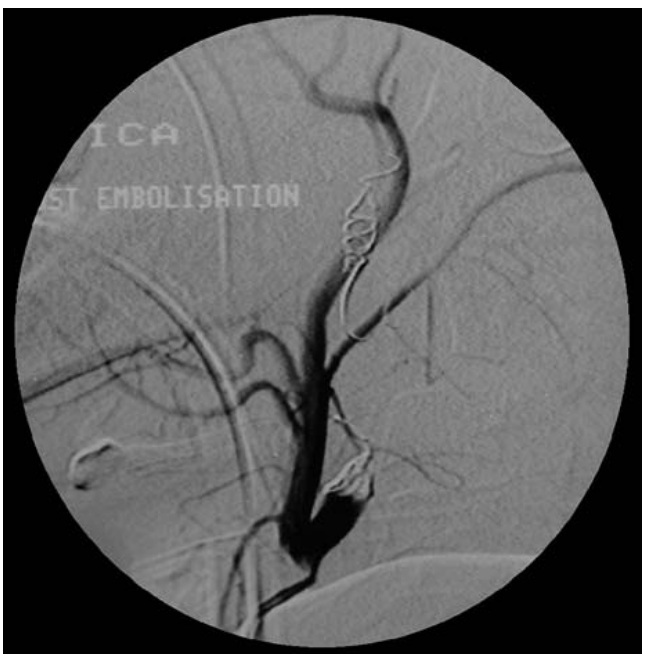

Figure 38.5 Trapped false aneurysm and fistula (Figure 38.4), with coils by endovascular technique.

FUTURE RESEARCH

- Significance of delayed repair of cervical oesophageal injury.
- CT scan for initial evaluation of penetrating cervical injury.
- MRI scan for initial evaluation of penetrating cervical injury.
- Endovascular intervention for vascular trauma.

KEY POINTS

- Properly executed, selective management of penetrating injuries of the neck is as safe as mandatory exploration.
- Trauma centres need to design their management protocols in accordance with their investigative and therapeutic capabilities.

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CHAPTER 39

BENIGN NECK DISEASE

Ricard Simo, Jean-Pierre Jeannon and Enyinnaya Ofo

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SEARCH STRATEGY

Data presented in this chapter are based on a Medline search using keywords listed in the chapter. The main terms included, congenital neck masses and acquired neck masses, inflammatory neck masses, and neck abscesses. It included diagnosis, surgery and management. The evidence of this chapter is mainly evidence levels 3 and 4 with some level 2 evidence. The clinical recommendations are predominantly B and C.

INTRODUCTION

Neck masses or swellings are a common occurrence. In the adult population, approximately 75% of non-thyroid neck masses are neoplastic,[1, 2] and of these 80% are metastatic. Around 75% of these metastatic neck masses are caused by a primary tumour located above the clavicle. In children under 15 years, 90% of neck masses are benign and of these up to 55% may be congenital.[1, 3, 4]

Benign neck masses may be classified as congenital or acquired. The latter group are often enlarged lymphadenopathy, but there may be a wide range of different pathologies involved. The introduction of fine-needle aspiration biopsy / cytology (FNAB / FNAC) with or without the use of ultrasound scan (USS) guidance has now become the gold standard investigation.[5–7]

The evaluation and management of patients presenting with a neck lump should include a systematic and uncompromising clinical approach.[2, 8–10] This must include a thorough history, examination of the upper aerodigestive tract and head and neck, followed by relevant investigations, which may include blood tests and radiological imaging.

History

This should include age, sex, past medical history, travel abroad, the mode of onset and duration of neck mass, associated symptoms including dysphonia, dysphagia, odynophagia, sore throat, referred otalgia, nasal obstruction, cranial nerve neuropathies, weight loss, anorexia, malaise and night sweats.

Examination

The examination should include an inspection of the skin over the skull, face, neck, and of the ears, nose, oral cavity and oropharynx. The fibre-optic endoscope should be used to inspect the nasal cavity, nasopharynx, oropharynx, larynx and hypopharynx.[2, 10, 11] The neck should be examined in a systematic fashion and the number, size, site, shape, texture and involvement of the skin and the deep cervical structures noted. Additionally, while concentrating on the head and neck as a source to explain the presence of a neck mass, it is frequently worth extending the general physical examination to include the chest and breasts in women, including the axillae. Examination of the neck is addressed extensively in Chapter 36, Clinical examination of the neck.

Investigations

The investigations of patient with a neck lump should be tailored to each individual case. All patients with neck lumps should as a minimum be considered for: full blood count (FBC), chest X-ray (CXR) and utrasound guided FNAB / fine-needle aspiration cytology (FNAC).

If an inflammatory mass is suspected, especially in a young patient, the above investigations together with an erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), Epstein–Barr virus (EBV) and cytomegalovirus (CMV) titres, liver function tests (LFTs), lactate dehydrogenase (LDH), Brucella, *Bartonella henselae* and toxoplasma serology may be advisable.[1, 9]

Once a clinical or tissue diagnosis has been made, it is possible to determine what, if any, further tests or imaging is required. If the diagnosis is infective or inflammatory a plain chest X-ray or no further imaging may be indicated. If a neoplastic lesion is diagnosed, computerized tomography scanning (CT), magnetic resonance scanning (MR) and positron emission tomography (PET) scanning alone or a combination may be performed. See details in Chapter 37, Imaging of the neck.[1]

A basic understanding of the different pathologies presenting as a neck lump is essential to direct adequate investigations and conclude an accurate working diagnosis without compromising the patient's clinical outcome. Occasionally, the clinician needs to be conscious that a working diagnosis may be incorrect;[12] hence it is paramount that patients are reviewed frequently during the early stages, to ensure resolution of the mass, if that is the expected outcome, or referral to a specialist for a second opinion if the anticipated diagnosis has not be confirmed, or doubts in the diagnostic accuracy still persist.

CONGENITAL NECK MASSES

LYMPHANGIOMAS

Lymphangiomas are degenerative lesions arising from lymphatics, and can be classified as: simple lymphangiomas, cavernous lymphangiomas and cystic hygromas.[13–16]

Lymphangioma simplex These are also called capillary lymphangiomas. They are composed of thin-walled capillary-sized lymphatic channels, usually asymptomatic and present as a pale, small vesicle-like lesions visible on the skin or oral cavity.

Cavernous lymphangioma Cavernous lymphangioma represent 40% of all lymphangiomas, composed of dilated lymphatic spaces, often with a fibrous adventitia, typically occurring in the tongue, cheeks and lips, and present as a painless diffuse swelling.

Cystic hygroma Cystic hygroma are composed of cysts and sinuses, varying in size from a few millimetres to several centimetres in diameter, usually presenting as a cystic mass containing eosinophilic acellular lymph fluid.

AETIOLOGY

The lymphatic system arises from five primitive sacs (two jugular sacs, two posterior sciatic sacs and a single retroperitoneal sac) developed from the venous system. Endothelial buds from these extend centrifugally to form the peripheral lymphatic system. Two principal theories have been postulated to explain the origin of lymphangiomas:[17, 18]

- Sequestration of lymphatic tissue derived from segments of the primitive sacs, which retain the proliferative growth potential and bear no connection with the normal lymphatic system
- Endothelial fibrillar membrane proliferation from the walls of the cyst, which penetrate the surrounding tissue along the lines of least resistance between muscles and vessels, canalize and produce more cysts.

CLINICAL FEATURES

Although congenital and in most cases present at birth, sometimes they can manifest for the first time in young adults. They can appear anywhere in the head and neck. On palpation they feel cystic and transilluminate. They may remain static or involute, but in some cases they gradually increase in size and occasionally, especially after internal haemorrhage or infection, can grow rapidly potentially risking life-threatening airway obstruction.[13, 19]

DIAGNOSIS AND INVESTIGATIONS

The diagnosis is usually made on clinical grounds but CT and MRI scanning will more accurately determine the size, exact anatomical location, and relationship with important structures as well as aiding surgical planning.[13, 19]

TREATMENT

The management of these lesions is difficult and challenging and many treatment modalities have been described over the years. The treatment strategy varies depending on the anatomical location, size and involvement of surrounding structures. Observation has been proposed by Broomhead[20] as up to 15% of patients may have spontaneous regression. Repeated aspirations may be helpful in the event of rapid increase in size causing pressure symptoms whilst awaiting definitive treatment. Injection of sclerosants such as bleomycin, tetracyclines and alcohol has been suggested, but internal scarring is reported to be unpredictable resulting in difficulty with any subsequent surgery and it is not currently recommended. The intra-lesion injection of OK-432 (Picinabil) has shown promising results.[21, 22] It causes an inflammatory reaction and thrombosis with subsequent necrosis. Surgical excision remains the treatment of choice but it is challenging and is therefore best undertaken by experienced surgeons in specialist centres.[17] Surgery can be helped by the injection of methylene blue into the lymphatic spaces (**Figure 39.1**).

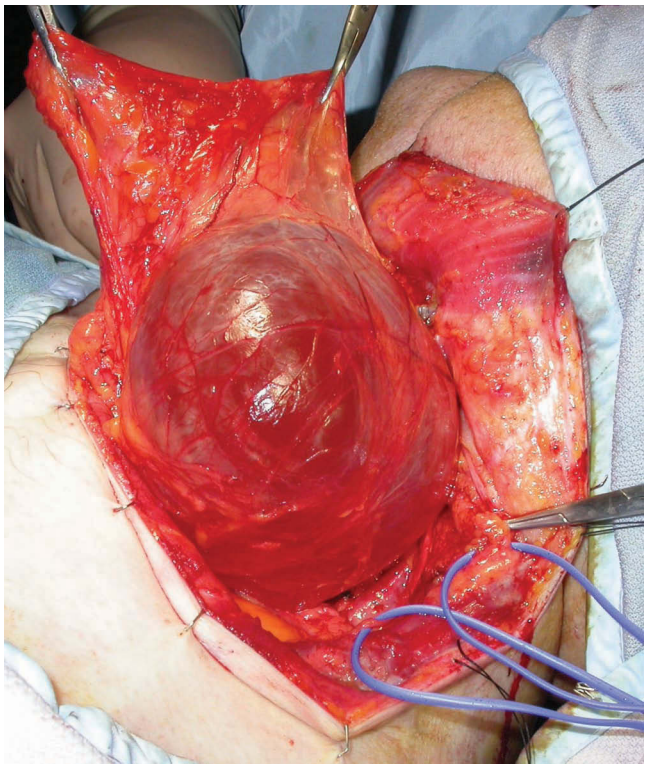

Figure 39.1 Operative picture of a lymphangioma of the supraclavicular region.

DERMOID CYSTS

Dermoid cysts are classified as epidermoid, true dermoid and teratoid cysts, depending on the types of tissues identified pathologically within them.[23] Twenty per cent of all dermoid cysts are found in the neck and 30% of these in the face. They make up 28% of all midline cysts, with no sex predominance.

Epidermoid cysts contain only skin and no other adnexal structures. They are lined with squamous epithelium with or without keratinous material. These are the most commonly encountered variety.

True dermoid cysts are lined with squamous epithelium and contain skin with appendages such as hair, hair follicles, sebaceous glands and sweat glands.

Teratoid cysts are lined either with squamous or respiratory epithelium. They contain all three embryological elements; ectodermal, endodermal and mesodermal elements such as nails, teeth, brain and glandular tissue.

AETIOLOGY

These lesions develop because of ectodermal differentiation of multipotential cells trapped at the time of closure of the anterior neuropore, especially along the lines of fusion, hence their being located along the midline of the neck. In the head and neck other areas of tissue fusion may present with dermoid cysts, such as external angular dermoids, and the nasal dorsum.[23]

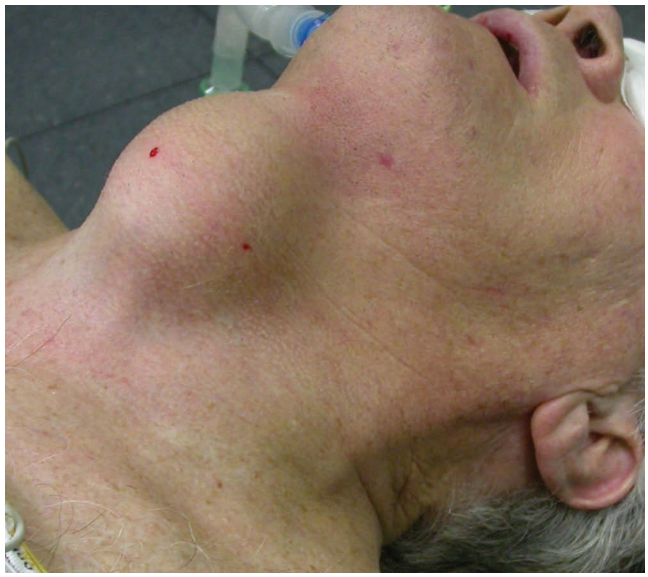

Figure 39.2 Thyroglossal cyst.

CLINICAL FEATURES

The peak age of incidence is usually the second and third decade. They can present as a cystic or solid painless mass, usually in the submental region, above or below the mylohyoid muscle. They may infrequently manifest as an acute inflammatory swelling associated with infection (**Figure 39.2**).

DIAGNOSIS AND INVESTIGATIONS

Diagnosis is suggested by the patient's age, the clinical location, and nature of presentation. Ultrasound-guided FNAC may be useful in the diagnosis of these lesions. Cross-sectional imaging such as a CT and MRI can help delineate the extent of large lesions, and aid surgical planning.

TREATMENT

Complete surgical excision is the treatment of choice.[23]

THYROGLOSSAL DUCT CYSTS

Thyroglossal duct cysts are the most common upper neck midline lesion accounting for almost one-third of all congenital neck masses.[24] They can present as a mass or lump, at any level between the foramen caecum and the upper mediastinum, with the majority presenting about the level of the hyoid bone. They are usually sporadic but a rare familial variant has been documented, identified as an autosomal dominant condition in pre-pubertal girls. Thyroglossal duct carcinoma, although rare, may present and be identified by the pathologist in a thyroglossal duct cyst.[25, 26] This is described in the section on thyroid malignancies.

AETIOLOGY

Embryologically the thyroid gland originates from the floor of the primitive pharynx between the first and second

pharyngeal pouches. In addition to the major median swelling, there are smaller paired lateral pouches, which contribute to the parafollicular or calcitonin-secreting C cells. The median pouch loses its lumen, about the 5th week of gestation and breaks into fragments, the lower end dividing into two portions that become the lobes of the thyroid gland. Thyroglossal duct cysts arise from epithelial cells when they cease to remain inactive. The stalk usually atrophies during the 6th week but should it persist as a patent tract, it becomes a thyroglossal duct along which cysts can develop. It may run from the thyroid gland inferiorly, upwards and in the region of the hyoid bone, and the tract may be located behind, through or in front of the hyoid, ending deeply in the junction of the anterior two-thirds and posterior one-third of the tongue, at the foramen caecum. The mechanisms involved in the development of cystic changes is not fully understood.[27] A fistula usually arises from spontaneous drainage of an abscess or more commonly following attempted drainage of a misdiagnosed midline neck abscess, or as a result of inadequate surgical excision associated with leaving an intact hyoid bone.

CLINICAL FEATURES

The majority (~95%) of thyroglossal cysts present as an asymptomatic cystic mass at or about the level of the hyoid bone. It moves on swallowing or on protrusion of the tongue. Up to 5% of these cysts present as an acute inflammatory episode with an infection, and 15% may have an associated discharging fistula.[28] There is no sex preponderance. The mean age of presentation is 5 years, with a range between 4 months to old age. Ninety per cent are in the midline but 10% may be to one or other side, with 95% of these being in the left side; 75% are pre-hyoid with the remaining 25% located above or below the hyoid, and rarely can be found within the mediastinum[24, 29] (**Figure 39.3**).

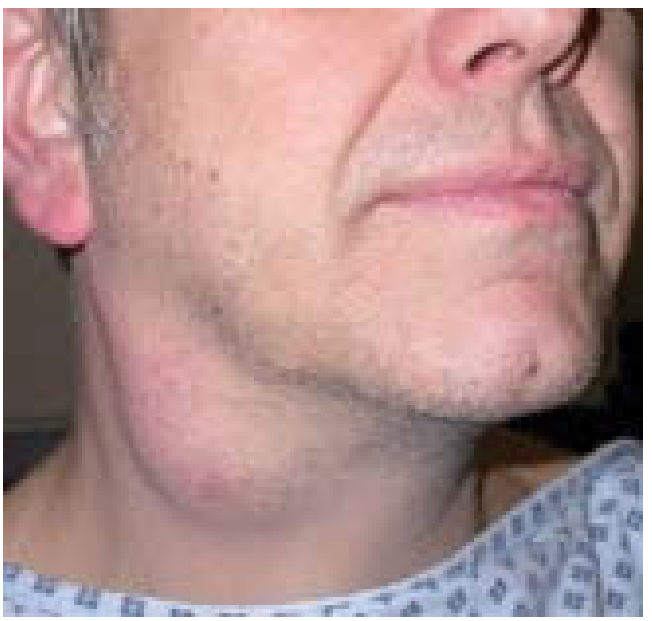

Figure 39.3 Right branchial cyst.

DIAGNOSIS AND INVESTIGATIONS

Patients with suspected thyroglossal duct cysts should be investigated with thyroid function test and ultrasound guided FNAC. The TSH and T4 levels will determine the thyroid status of the patient. USS may help with the location and diagnosis of the cyst, and will also confirm the presence of a normal thyroid gland in its expected anatomical position. FNAC will demonstrate cystic contents containing colloid. Isotope scan with either Tc^{99} or I^{123} may be useful if the cyst is located above the hyoid or in the posterior tongue, with a view to identifying or excluding the presence of a lingual thyroid. CT or MRI scanning should be considered in the presence of large cysts, when malignancy is suspected and when the possibility of a lingual thyroid has been considered.[30]

TREATMENT

Surgical excision is the treatment of choice, as there is a high probability the cyst may become infected, resulting in loss of normal tissue planes, or scarring of the neck skin and the occurrence of recurrent cyst enlargement causing patient discomfort.[24, 31] The Sistrunk procedure was described in 1920,[32] which resulted in a permanent cure for the majority of cases. Previously the hyoid bone was not excised resulting in recurrence rates of up to 50%,[33] with associated infections.[34] A modification of the Sistrunk technique is currently employed as the standard surgical procedure, without the need to excise the tongue base epithelium. The excision is performed through a transverse midline neck incision just below the cyst. The lesion is dissected from the infra-hyoid strap neck muscles and the laryngeal cartilages. The dissection then proceeds upwards to the region of the hyoid bone. At this point the suprahyoid muscles, i.e. mylohyoid, geniohyoid and genioglossus, are detached from the hyoid bone, while the middle third of the hyoid bone, between the lesser cornu, is cut and mobilized in continuity with the soft-tissue specimen, which includes the thyroglossal duct cyst. The completion of surgery involves further dissection upwards, into the tongue base, to include a core of tissue that should incorporate the tissue tract or raphe between the mylohyoid muscles, a portion of each genioglossus muscles up to the region of the foramen caecum. The technique as described has resulted in a significant reduction in recurrence rates, when compared with simple excision or removal of the cyst alone (Shalang Procedure) (**Figure 39.2**).[35]

Treatment of recurrent cysts and fistulae

Up to 8% of thyroglossal cysts may recur following adequate surgical excision.[36] If a substandard excision, without removal of the central portion of the hyoid bone, had been performed, the classic Sistrunk procedure should be undertaken. However, further surgery following a Sistrunk procedure may be difficult. In these cases, the previous incision scar should be excised and a central compartment neck dissection performed, with excision of the scar tissue up to the foramen caecum.[37, 38]

BRANCHIAL CYSTS

The word 'branchial' is derived from the Greek '*bragchia*' meaning gills. Branchial cysts appear as a developmental failure of the branchial apparatus. Branchial anomalies account for up to 19% of all paediatric cervical masses.[39] They often manifest in young adults with a peak incidence in the third decade. Cysts are usually lined by stratified squamous epithelium except in 10% of cases that may have respiratory epithelium instead; 80% have lymphoid tissue in the outer wall and contain straw-coloured fluid in which cholesterol crystals are found.

AETIOLOGY

Four theories have been suggested to explain the origin of branchial cysts.[40, 41]

Branchial apparatus theory

This theory suggests that branchial cysts represent remains of pharyngeal pouches or branchial clefts, or a fusion of these two elements. The development of the branchial apparatus extends from the 3rd to the 8th week of gestation. This theory would suggest that cysts should be present at birth, whereas the peak incidence is usually in the 2nd to 3rd decade.

Cervical sinus theory

This theory advocates that branchial cysts represent the remains of the cervical sinus of His, which if formed by the second arch growing down to meet the fifth arch. The second arch mesoderm almost covers the neck entirely and forms the platysma muscle.

Thymopharyngeal duct theory

This theory suggests that the cysts are remnants of the original connection between the thymus and the 3rd branchial pouch from which it takes origin. However, a persistent thymic duct has never been described and there has never been a branchial cyst found deep to the thyroid gland.

Inclusion theory

This theory postulates that branchial cysts are epithelial inclusions within a lymph node. This theory is supported by the fact that most branchial cysts have lymphoid tissue in their wall and have been reported in the parotid and the pharynx. This theory also explains why most branchial cysts have no internal opening, are almost unknown in neonates, while the peak age of presentation is much later in life, compared to that seen for most other congenital lesions.

CLINICAL FEATURES

Sixty per cent are located in the upper third of the neck, at the anterior margin of the sternocleidomastoid muscle, although they have been reported in any site of the neck including the parotid gland (**Figure 39.3**).[39] The presentation is a persistent neck swelling in 80% (with 20% intermittent in nature),[42] with 70% appearing cystic although up to 30% may feel solid. In nearly 40% of cases, a history of upper respiratory tract infection prior to noticing the mass can be elicited. Inflamed cysts may be complicated by abscess formation with the possibility of rupture.

DIAGNOSIS AND INVESTIGATIONS

All patients with a suspected branchial cyst should be investigated with at least a FBC and ultrasound-guided FNAC. Ultrasound-guided FNAC yields acellular fluid with cholesterol crystals on microscopy examination. However cytological findings should be interpreted cautiously, given that squamous debris may suggest malignancy. If lymph nodes are necrotic, as seen in squamous cell carcinoma and tuberculosis, they may be difficult to distinguish sonographically from a second branchial cleft cyst, but FNB is usually helpful. CT and MRI scanning is a useful investigation for large cysts to allow surgical planning (**Figure 39.4**).

TREATMENT

Surgical excision is the treatment of choice.[39] This is indicated as branchial cysts have a tendency to become infected, can increase to a large size causing local discomfort, pressure symptoms and obvious cosmetic deformity. The procedure is initiated by a transverse cervical incision made on the neck skin crease overlying the cyst. The platysma is incised and sub-platysmal flaps are elevated. The cervical fascia is incised over the anterior border of

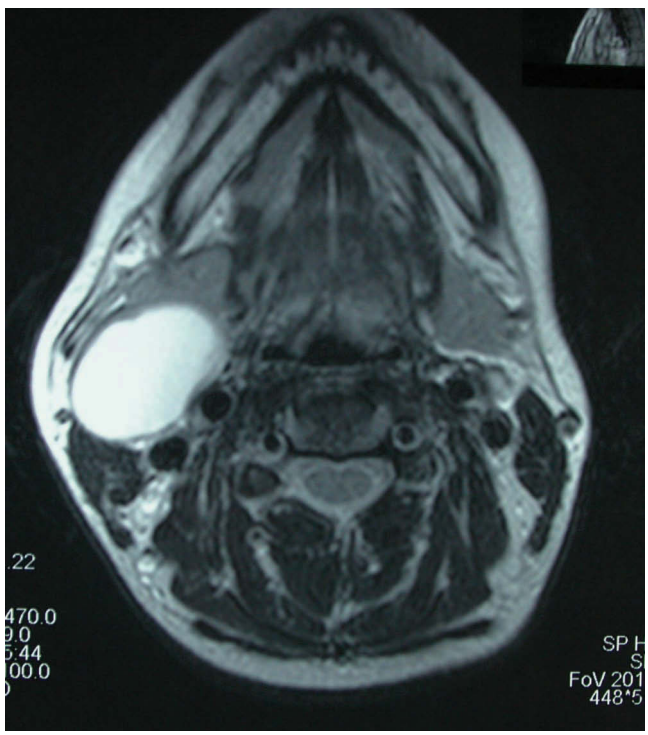

Figure 39.4 MR scan demonstrating a large right branchial cyst.

the sternocleidomastoid muscle, which is retracted laterally. The cyst is then identified and dissected from its fascial attachments and capsule ensuring that the cyst wall is not ruptured. During the dissection the carotid sheath and its contents should be identified and mobilized out of the surgical area. In addition, the marginal branch of the facial nerve, vagus, accessory and hypoglossal nerves should be identified and preserved. The cyst is excised completely and there is usually no need to look for a tract although the tail of the cyst may need to be dissected from the tail of the parotid gland or parapharyngeal space.

KEY POINT

- In patients over the age of 35, cystic neck lumps should be considered metastatic unless proven otherwise. These are usually seen with high-risk HPV-related head and neck squamous cell carcinomas.

BRANCHIAL FISTULAE AND SINUSES

Branchial fistulae are congenital defects consisting of a skin-lined tract, opening internally as a slit on the anterior aspect of the tonsil fossa if it is of second arch origin. The external opening is at the anterior border of the sternocleidomastoid muscle, at the junction of its middle and lower thirds.[27]

Branchial sinuses or branchial pits open along a line between the tragus and the sternoclavicular joint at the anterior border of the sternocleidomastoid muscle but with no internal opening.

AETIOLOGY

They arise from failure of complete development of the branchial apparatus including the first, second, third and fourth arches. During the 4th week of intrauterine life, six branchial arches develop as neural crest cells migrate cranially. During the 5th week, the second branchial arch grows over the third and fourth branchial clefts, forming a cervical sinus. Failure of the cervical sinus to close allows for potential communication with the second branchial pouch in the area of the tonsil fossa, the third pouch in the area of the larynx, and the fourth pouch opening in the pyriform fossa.[27]

CLINICAL FEATURES

Most patients are usually young infants with a discharging sinus, which may or may not have an internal fistulous opening. Clinically, second branchial cleft fistulae are the most common. They have a cutaneous opening along the anterior border of the sternocleidomastoid, usually at the junction of the middle and lower thirds, tracking up between the internal and external carotid arteries ending in the tonsillar fossa. Third and fourth branchial fistulae are rare, opening low in the neck and ending in the pyriform sinus, with an opening that is sometimes visible on endoscopic examination.[43]

DIAGNOSIS AND INVESTIGATIONS

The diagnosis is made on clinical grounds. A contrast swallow or CT fistulogram may be helpful to determine the pathway of the tract, differentiate a sinus from a fistula and aid surgical planning (**Figure 39.5**).

TREATMENT

Surgical excision is the treatment of choice.[44] The excision is performed in a stepladder fashion, removing the mouth of the sinus with an ellipse of neck skin. The tract is followed upwards as high as possible and then another transverse cervical or cervico-facial incision is made. The dissection is then continued to the tonsillar region where the tract usually disappears and should be ligated before it avulses, in order to minimize recurrence of symptoms (**Figure 39.6**).

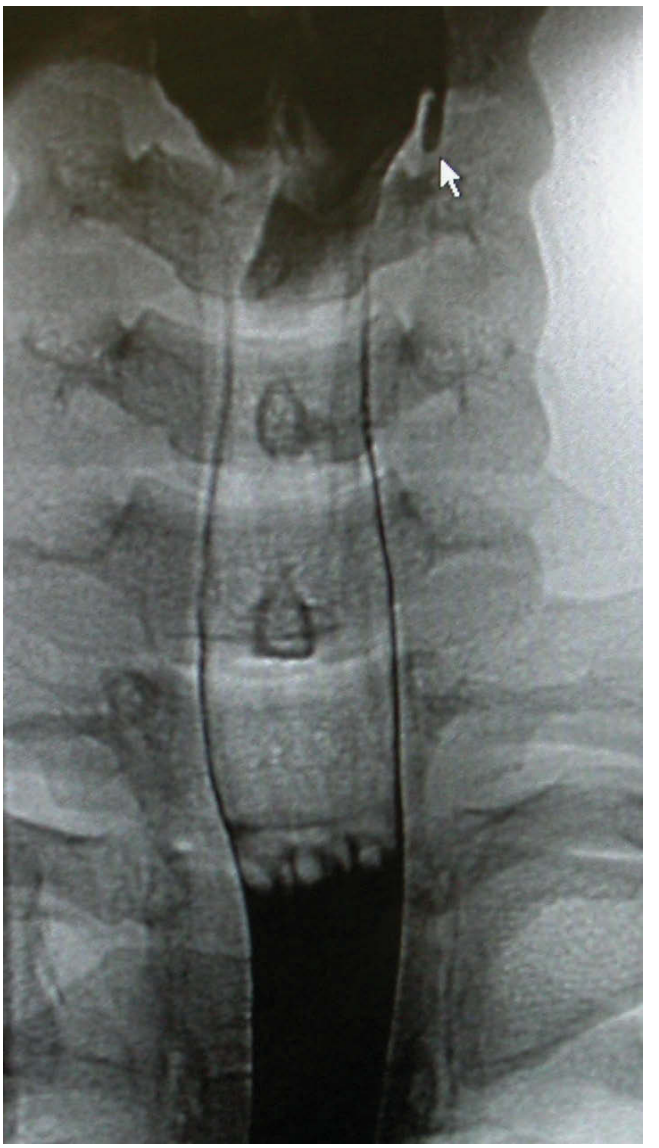

Figure 39.5 Fistulogram of a left branchial fistulae.

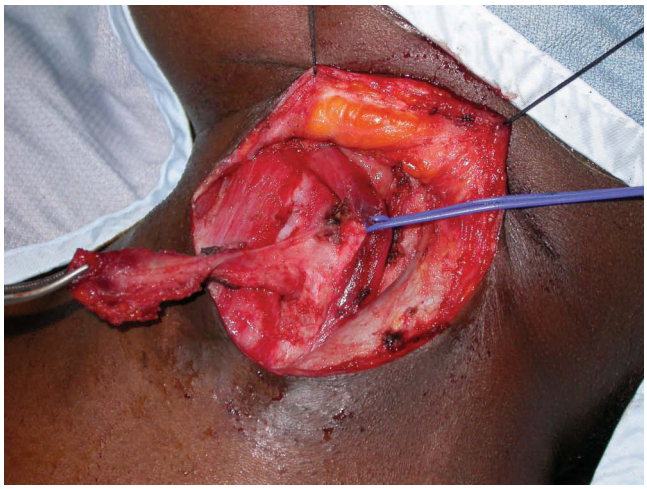

Figure 39.6 Left branchial fistula tract emerging between the constrictor muscles and deep to the omohyoid muscle.

ACQUIRED NECK DISEASES AND MASSES

NON-INFLAMMATORY NECK MASSES

Sebaceous cysts

Sebaceous cysts are skin appendages lesions occurring mainly where there are sebaceous glands and are commonest in hairy skin, particularly in the beard region and scalp.

AETIOLOGY

These cysts develop when the duct of a sebaceous skin gland, responsible for the production of oily sebum protecting the skin, becomes blocked. The retained secretions distend the gland causing progressive enlargement of the cyst.

CLINICAL FEATURES

The lesions can be single or multiple, and of different sizes. They tend to be spherical, smooth and well defined, stretching the overlying skin and the opening of the blocked duct is often visible as a 'punctum'. The cyst may discharge in which case the creamy secreted dry material may accumulate in the centre to form a sebaceous horn, and sebaceous cysts also have a tendency to become infected.

DIAGNOSIS AND INVESTIGATIONS

Sebaceous cysts often display very distinct clinical features and rarely require investigation. They have a non-specific sonographic appearance and FNB/FNAC is not necessary unless there is clinical doubt.

TREATMENT

Surgical excision is the treatment of choice as they are unsightly, have a tendency to grow, burst, get infected and recur. Excision should be done very carefully ensuring that the punctum, and scar if they have been previously incised and drained due to infection, is excised with a small ellipse of healthy skin, to avoid leaving part of the cyst capsule which will lead to the recurrence of the lesion.[45]

Acquired dermoid cysts (implantation dermoids)

Dermoid cysts are usually solitary, with solid and cystic areas containing skin appendages.

AETIOLOGY

Acquired dermoids occur due to a penetrating injury or following surgery resulting in the implantation of dermal or skin structures deep into the subcutaneous tissue.

CLINICAL FEATURES

These cysts present at the site of a penetrating injury and often display solid and cystic areas containing sebaceous material.

DIAGNOSIS AND INVESTIGATIONS

The diagnosis is often made on clinical grounds however ultrasound-guided FNAC may be helpful in some cases where the history of injury is not clear.

TREATMENT

Surgical excision is the treatment of choice. The incision should include the injury tract that should be completely excised in continuity with the cyst to avoid recurrence.[46]

Pilomatrixoma or calcifying epithelioma of Malherbe

Pilomatrixoma is a benign tumour of the prickle cell layer of skin, first described by Malherbe and Chenantais in 1880 as a calcified epithelioma.[47–49] It is most frequently seen in the first two decades of life with two-thirds of these occurring in patients under 10 years of age and is more common in females, with a female preponderance of 3:2. The majority of these tumours (68%) occur in the head and neck region. Malignant transformation has been described but is very rare.

AETIOLOGY

The aetiology is unknown although an episode of local inflammation or trauma may precede their development.

CLINICAL FEATURES

Pilomatrixomas are usually solitary and present as a firm, nodular superficial lesions measuring up to 3 cm in size. There is usually no discolouration but if situated superficially a blue-red colour may be seen.

DIAGNOSIS AND INVESTIGATIONS

Pilomatrixomas have very distinct clinical features. If the diagnosis is suspected, FNAC can be performed. Cytopathological features include the identification of basaloid and squamous cells, calcium deposits and foreign body giant cells.[49]

TREATMENT

Surgical excision is the treatment of choice if the lesion is bothersome or there is doubt about diagnosis. The excision must be carefully performed in the same manner as for an epidermoid cyst as leaving part of the capsule will result in recurrence of the lesion.[50]

Lipomas

Lipomas are benign lesions of the adipose layer. The adipose cells are organized into large lobules divided by loose fibrous septa. Lipomas can be multiple and occasionally can be painful (Dercum's disease). Although the majority of lipomas are sporadic a minority can be familial.[51] The most common familial lipomatosis affecting the head and neck is Madelug's lipomatosis. In the neck region, lipomas may be subfascial or arising within the muscles. They grow very slowly and have a very low risk of malignant transformation.

AETIOLOGY

The aetiology is unknown, however, a history of preceding trauma which leads to breakdown of the adipose layer and abnormal growth has been suggested.[52]

CLINICAL FEATURES

Lipomas usually occur in adults and have a variable size. The tumour has a smooth, lobulated surface with a well-defined edge. They tend to be soft, and as they lie below the dermis, the overlying skin can be moved above the lesion.

DIAGNOSIS AND INVESTIGATIONS

Lipomas have characteristic appearances on USS, and do not require FNAC, unless risk of malignant transformation is suspected. For large lipomas, CT and MRI scanning may be useful in assessing the anatomy and aid surgical planning.[53]

TREATMENT

Surgical excision is the treatment of choice when the lesion is of a large size causing an obvious cosmetic deformity, when there is suspicion of malignancy, or due to patient choice.[53]

INFLAMMATORY NECK MASSES

Acute cervical lymphadenitis

Acute cervical lymphadenitis is common, especially in the paediatric population.[54] It occurs due to viral or bacterial infection in the upper aerodigestive tract, ears, or the skin of the head and neck.

CLINICAL FEATURES

The mass is usually painful and may result in an abscess, in which case the mass appears fluctuant. The patient may be toxic, and the primary infective process is usually evident, although in small children it is not always clear.[55]

DIAGNOSIS AND INVESTIGATIONS

The diagnosis is made on clinical grounds. If the infective episode is severe and the child requires hospital admission, basic haematological and biochemical investigations such as white cell count and CRP levels may aid in diagnosis. Usually, other investigations are not required unless there is clinical suspicion that the patient is developing an abscess, or there are concerns of an underlying neoplastic process. In these situations ultrasound-guided FNAC may aid the diagnosis.

TREATMENT

Treatment is initially empirical, with supportive and broad-spectrum antibiotic therapy, if a bacterial infection is suspected or diagnosed.[56]

Infectious mononucleosis

Infectious mononucleosis or glandular fever is a viral infection caused by EBV that usually affects adolescents and younger adults.[57, 58] EBV infection is also associated with the development of EBV-associated lymphoid or epithelial cell malignancies such as Hodgkin lymphoma, Burkitt lymphoma, nasopharyngeal carcinoma and multiple sclerosis.

AETIOLOGY

EBV is a gamma-herpes virus that infects over 90% of the human population worldwide. It is usually transmitted between individuals in saliva, and establishes replicative infection within the oropharynx as well as life-long latent infection of B cells. Primary EBV infection generally occurs during early childhood.[59]

CLINICAL FEATURES

Primary EBV infection may be asymptomatic or results in a mild self-limiting illness characterized by fever, tonsillitis and lymphadenopathy. If delayed until adolescence or later, it can be associated with the clinical syndrome of infectious mononucleosis, which is characterized by fever, pharyngitis, lymphadenopathy, especially cervical, and malaise. Five per cent of patients develop a maculopapular rash and up to 50% of patients may develop palatal petechiae, acute bacterial tonsillitis usually with a grey fibrinous exudate, splenomegaly and hepatomegaly. In severe cases or in immunocompromised patients, autoimmune haemolytic anaemia, thrombocytopenia, splenic rupture, encephalitis, cranial nerve paralysis and acute

upper airway obstruction as a result of significant tonsillar hypertrophy can develop.[60, 61]

DIAGNOSIS AND INVESTIGATIONS

The diagnosis is made on clinical grounds. The FBC will show more than 50% of mononuclear cells and over 10% atypical lymphocytes. The ESR and CRP will be elevated. Monospot and Paul Bunnell tests will be positive, but may also be negative, especially in the first 2 weeks of the disease. Hepatic enzymes may also be elevated.

TREATMENT

The management is largely supportive with conservative measures, such as rest and hydration. Avoidance of contact sports and heavy lifting is advised for at least 6 weeks, and abstainance from alcohol whilst LFTs remain abnormal.

Broad-spectrum antibiotic therapy may be useful in cases of secondary bacterial infective tonsillitis but ampicillin and its derivatives should be avoided as patients may develop a maculopapular rash. Corticosteroid therapy is advisable in cases of impending airway obstruction, thrombocytopenia and haemolytic anaemia as well as other complications, such as cranial nerve paralysis.[62] Antiviral chemotherapy with acyclovir or famcyclovir has been reported to help in some cases.

Cat scratch disease

Cat scratch disease mainly affects children and young adults with a peak of incidence between 2 and 14 years of age.[63] The disease is more common in the USA where over 24 000 people may be affected every year, but also affects Europe, Africa, Australia and Japan.

AETIOLOGY

Cat scratch disease is caused by the Rickettsia *Bartonella* sp. *Bartonella henselae* is the most common species to cause the widest spectrum of diseases in humans, and cats especially kittens are the main reservoir.

CLINICAL FEATURES

Cervical lymphadenopathy is preceded by erythematous papulae at the site of inoculation. Systemic symptoms such as fever, malaise, anorexia, headache and splenomegaly can occur, but tend to be more common in the immunocompromised patients.

DIAGNOSIS AND INVESTIGATIONS

Serological testing for *Bartonella henselae* is both sensitive and specific for cat scratch disease.[64, 65] More recently polymerase chain reaction RNA of the bacteria has been used for diagnosis.[65]

TREATMENT

Several antibiotics such as gentamicin, rifampicin, ciprofloxacin, and especially azithromycin which is associated with rapid resolution, have been advocated.[65] However, antibiotic use in cat scratch disease without systemic symptoms remains controversial given that infections may resolve without treatment.

Cervical necrotizing fasciitis

This is a rare, but life-threatening infection, which causes progressive necrosis of the skin and subcutaneous tissues.

AETIOLOGY

It results from an odontogenic[66] or tonsillar bacterial infection or may be a complication following deep space neck infections or surgery.[67, 68] *Streptoccocus pyogenes* or *viridans* and mixed anaerobes are the most common aetiological agents.[67]

CLINICAL FEATURES

The diagnosis is made on clinical grounds, with characteristic features such as initial cutaneous cellulitis with disproportionate pain that progresses to necrosis of subcutaneous tissues and skin.

DIAGNOSIS AND INVESTIGATIONS

The white cell count and other inflammatory parameters are raised. An ultrasound or CT scan may show oedema and air pockets of the skin, which are diagnostic features.[67]

TREATMENT

If untreated, cervical necrotizing fasciitis can be fatal, hence early diagnosis and treatment are essential. Intravenous high-dose antibiotic therapy, against aerobic and anaerobic bacteria, with debridement of all necrotic areas, is mandatory.[66, 67]

Chronic cervical lymphadenitis

There is a wide range of chronic inflammatory conditions which may present with cervical lymphadenopathy. They are often associated with systemic symptoms such as malaise, weight loss, anorexia and night sweats, hence the clinical history is very important. These conditions include: HIV and AIDS, sarcoidosis, toxoplasmosis, actinomycosis and tuberculosis (TB). In all cases, excluding TB, lymph node enlargement may be non-specific, hence clinical diagnosis may be difficult.

HIV-AIDS

Acquired immunodeficiency syndrome (AIDS) is a viral disease caused by human immunodeficiency virus (HIV). The infection is classified as:

1. acute infection or seroconversion illness
2. asymptomatic infection
3. persistent generalized lymphadenopathy (PGL)
4. full blown AIDS.

AETIOLOGY

The HIV virus is transmitted via contaminated blood or human secretions. It is prevalent in homosexuals, promiscuous heterosexuals and intravenous drug-abusers.

CLINICAL FEATURES

Up to 30% of seroconverted patients develop PGL and it may be the first manifestation of the disease. As with the acute seroconversion illness, PGL tends to be non-specific and it is characterized by multiple diffuse lymphadenopathy involving two or more extra inguinal sites for <3 months. It may also be an early sign of HIV infection and associated with other manifestations of the disease (**Table 39.1**).[69, 70]

INVESTIGATIONS

When suspected, HIV serology is indicated and diagnostic. FNAC will help the diagnosis of PGL and also assist in elucidating other causes of infection such as TB, Kaposi sarcoma (KS) or non-Hodgkin lymphoma (NHL).

TREATMENT

CD4+ lymphocyte count is the most important reference factor for initiating ART in asymptomatic patients. The large number of available drugs, the increased sensitivity of tests to monitor viral load, and the ability to determine viral resistance, has resulted in a more individualized approach to therapy.[71–73]

Tuberculous adenitis

TB is the oldest documented infectious disease. It is the world's leading cause of death from a single infective agent and is on the increase.[74, 75] Amongst the factors associated with reversal of a previous decline are; increased world travel and a rising incidence of immunodeficiency through HIV infections or intravenous drug abuse. Pulmonary TB is the most common manifestation but extra-pulmonary disease is also increasing in incidence with tuberculous adenitis, or historically named 'scrofula,' being the most common. The word scrofula comes from the Latin 'scrofulae' meaning brood sow. In the middle ages, it was believed that the 'royal touch' of the sovereign of England or France could cure the disease. It was therefore known as the King's Evil. The kings were thought to have received this power having descended from Edward the Confessor, whose legend states he received the power from Saint Remigius. Tuberculous adenitis can affect any lymph node group of the head and neck, including salivary glands and thyroid. Hence it is important to have a high index of suspicion especially in certain ethnic groups where TB may be endemic.

TABLE 39.1 Otorhinolaryngological manifestations of HIV infection

Candidiasis
Hairy leukoplakia
HIV-gingivitis
Necrotizing ulcerative gingivitis
Kaposi sarcoma
Non-Hodgkin lymphoma
Benign lymphoepithelial cyst parotid gland
Benign hyperplasia of the lymphoid tissue
Pneumocystic *carinii neumonia*
Tuberculosis
Opportunistic infections

AETIOLOGY

Mycobacterium TB is an obligate aerobe, non-spore forming slender rod. Humans are the only reservoir and it is usually acquired through contact from a TB infected patient via air-borne transmission. After a short period of replication in the lungs, silent dissemination occurs through the lymphohematogenous system to extra-pulmonary sites including the cervical lymph nodes. This pathophysiological process differs from non-tuberculous atypical mycobacterial adenitis (NTAMA) that is addressed later in this chapter.

CLINICAL FEATURES

Ninety per cent of patients have unilateral involvement mainly of the jugular chain of lymph nodes, followed by the submandibular triangle and the posterior triangle. The lymph nodes are usually firm, painless and present with a characteristic erythematous skin discoloration. If the disease has progressed without being diagnosed, they tend to fistulae, and present with an obvious discharging sinus, or form a 'cold' abscess, which suggests the clinical diagnosis. TB can also affect the ear, nose, pharynx, larynx, salivary and thyroid glands (**Figure 39.7**).[74, 76, 77]

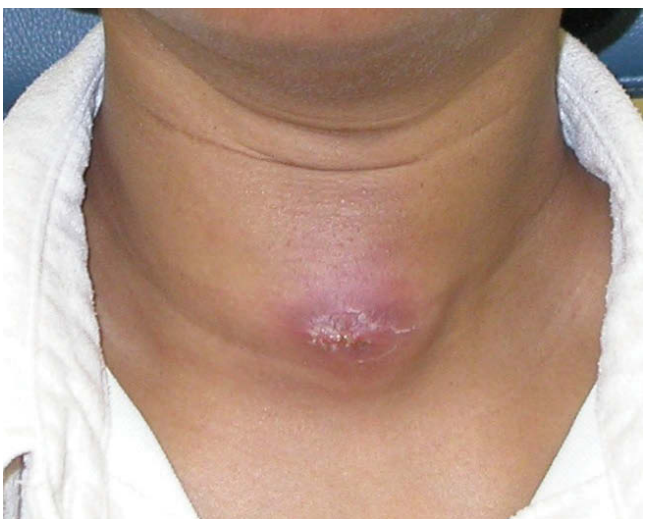

Figure 39.7 Cervical tuberculous adenitis with central necrosis (scrofula).

DIAGNOSIS AND INVESTIGATIONS

Head and neck TB can be very difficult to diagnose, as the clinical features may resemble neoplastic disease, especially when presenting as a single-organ involvement. FBC is non-specific and may be normal. ESR is often elevated. Chest X-ray is mandatory but only up to 20% of patients will have positive changes. Soft-tissue X-rays of the neck may show dystrophic calcification characteristic of TB infection. Mantoux and Heaf test may be non-diagnostic if the patient has been vaccinated against TB, but a grade IV skin reaction on this test may suggest active infection. USS of the nodes will often show multiple, matted nodes but may be non-specific. FNAC can reveal mycobacteria, but is only positive in up to 40% of patients,[78] however, the use of FNAC and polymerase chain reaction allows a quick and accurate diagnosis with high specificity (84%) and sensitivity (100%). Excision biopsy if possible, may be very difficult due to the matted nature of lymph nodes, with an increased risk of bleeding and nerve injury. Alternatively, incisional biopsy of affected nodes should be performed if there is already skin involvement. Samples should be sent for microbiology as well as histological analysis and this should provide the definitive diagnosis. Microbiology analysis may take up to 6 weeks to culture mycobacteria, which may delay treatment. HIV testing is advisable in all patients.[74–78]

TREATMENT

Suspected or proven active tuberculous adenitis is treated with a combination of antibiotics, using a multidisciplinary approach with involvement of respiratory or infectious diseases physicians amongst others.[74, 77] Increasing resistance is currently a significant problem and therefore chemotherapy should be adjusted according to sensitivity. Surgery has a limited role and should only be used as a diagnostic tool or in cases of residual disease.

Non-tuberculous atypical mycobacterial adenitis

Non-tuberculous atypical mycobacteria (NTAM) adenitis is increasingly common in the Western world, and the main difference from tuberculous infection is it tends to affect otherwise healthy immunocompetent children from middle-class families.[79]

AETIOLOGY

Mycobacterium avium and *Mycobacterium avium intracellulare* are the main two pathogens. The route of entry is usually through the oropharynx or the eye, from ingestion of contaminated soil leading to superficial lymphadenopathy in the neck.

CLINICAL FEATURES

Patients affected by NTM are usually young healthy children with multiple cervical lymphadenopathy, but without any symptoms or signs of systemic illness. The enlarged lymph nodes often adhere to skin causing a characteristic red-purple discolouration, with occasional abscess or sinus formation and scarring.[79–81]

DIAGNOSIS AND INVESTIGATIONS

The diagnosis is made on clinical suspicion and confirmation relies on isolating the organisms in culture either through microbiological swabs, FNAC or incisional biopsy.

TREATMENT

Most children may eventually develop their own immunity so a period of observation is advisable especially if the lesion is in the parotid gland. Antibiotic therapy with macrolides such clarithromycin or azithromycin with or without antituberculous therapy has been suggested.[82] In some studies resolution has been achieved in up to 67% of cases, without surgical excision. Surgical curettage with or without antibiotic therapy may be an option and has been used with some success in selected cases especially if full surgical excision may cause significant morbidity.[79] Surgical excision is the ultimate treatment of choice and appears to be more effective than antibiotic therapy alone.[79, 83, 84]

Brucellosis

Brucellosis is primarily a disease of domestic animals and causes contagious abortion or other reproductive problems in cattle (*Brucella abortus*), pigs (*B. suis*), goats (*B. melitensis*), dogs (*B. canis*) and sheep (*B. ovis*). Current pasteurization of dairy products, and other hygienic preventive measures, as well as adequate animal vaccinations has greatly reduced the incidence of the disease in Western countries.[85]

AETIOLOGY

Human spread of *Brucella* spp. occurs by direct contact of infected tissue with the conjunctiva or broken skin, by ingestion of contaminated meat or dairy products, or by inhalation of contagious aerosols.

CLINICAL FEATURES

The clinical features are often non-specific and some infections are subclinical. When the infection is clinically evident, most patients complain of night sweats, chills, undulating pyrexia and malaise. Up to 20% of patients will develop cervical lymphadenopathy and a similar percentage will have splenomegaly.[85]

DIAGNOSIS AND INVESTIGATIONS

When the diagnosis is suspected, blood cultures will often isolate the bacteria and provide a definitive diagnosis. Serology will also provide the diagnosis in those cases where the clinical picture is less obvious.

TREATMENT

This involves combination antibiotic therapy, as single-agent treatment is associated with a 30% risk of relapse. The current WHO recommendation is to use doxycycline 200 mg and rifampicin 900 mg daily for 6 weeks.[86]

Toxoplasmosis

AETIOLOGY

Toxoplasmosis is a worldwide infection caused by *Toxoplasma gondii*, a protozoan transmitted by the ingestion of cysts excreted in the faeces of infected cats, or from eating undercooked beef or lamb.[87]

CLINICAL FEATURES

Congenital infection usually causes hydrocephalus or microphaly. Acquired infections present with generalized malaise, myalgia, fever, cough and a maculopapular rash. If untreated, a chronic phase will develop which may be asymptomatic or present with isolated cervical lymphadenopathy. In immunocompromised patients especially with HIV-AIDS, it may cause encephalitis.[87]

DIAGNOSIS

The diagnosis is made on clinical history and complemented by serology, which will provide confirmation in the majority of cases.[87, 88] The white cell count will show lymphocytosis with atypical mononuclear cells. FNAC may suggest the diagnosis although may be non-specific. Lymph node biopsy will reveal features supporting the diagnosis of toxoplasmosis.[89] CSF analysis may demonstrate the parasite and confirm the diagnosis if there is central nervous system involvement.

TREATMENT

Where treatment is indicated a combination of sulphadimidine, pyrimethamine and folic acid is used.[87] The FBC should be monitored regularly until it becomes normal.

Actinomycosis

AETIOLOGY

Actinomycosis is a bacterial infection caused by *Actinomycosis israelii*, an anaerobic organism which is a commensal in the healthy oral cavity.[90] The organism may become pathogenic when the mucous membrane is injured. Infection is usually associated with severe dental caries and periodontitis.

CLINICAL FEATURES

Patients present with a firm indurated mass with ill-defined edges usually lateral to the mandible. If left untreated the infection may spread to adjacent tissues and may become bony hard. Once the infection is established multiple sinus may develop which discharge pus and watery fluid containing characteristic sulphur granules.

DIAGNOSIS AND INVESTIGATIONS

The diagnosis may be suspected on clinical grounds, which are usually typical. FNAC may show sulphur granules that are diagnostic. Tissue biopsy will again show characteristic colonies with sulphur granules, but the organism may be difficult to culture.[90]

TREATMENT

Therapy is with intravenous benzylpenicillin or cephalosporins in high doses that may be required for at least 6 weeks. However, longer courses of antibiotic treatment for up to 1 year may be necessary in resistant cases or immunocompromised patients. Removal of carious teeth is imperative to eliminate the site of origin of the infection.[90]

NECK ABSCESSES

In this section only the superficial soft tissue neck abscesses will be addressed as the deep neck infections will be addressed in Chapter 40, Neck space infections.

Superficial soft tissue neck abscesses

Cervical abscesses are relatively uncommon in comparison with the number of acute and chronic lymphadenitis that present in the paediatric and adult population. However, small children under the age of 4 years and immunocompromised patients appear to be more susceptible.

AETIOLOGY

Failure of patients to eliminate the organism at the site of attachment to the nasal or pharyngeal epithelium will result of spread of infection via lymphatics causing suppuration. The most common pathogens are: *Staphyloccoccus aureus*, *Streptococcus pyogenes* and in the paediatric population atypical mycobacteria.[56]

CLINICAL FEATURES

The development of the abscess is often preceded by an upper respiratory tract infection although on occasions this may not be obvious from the history, especially in the younger paediatric population.

DIAGNOSIS AND INVESTIGATIONS

Diagnosis is based on clinical suspicion. FBC, ESR and CRP are useful to ascertain the inflammatory origin and monitor progress. USS and CT scanning will be useful to determine whether the mass has a central area of necrosis that may require incision and drainage.

TREATMENT

The treatment involves a combination of supportive therapy, broad-spectrum antibiotics until culture and sensitivity

results are available, plus or minus surgical incision and drainage. Repeated needle aspiration is not usually helpful unless the abscess is arising from a thyroglossal duct cyst in which case incision and drainage is reserved as a last resort after antibiotic therapy and repeated aspiration has failed.[56]

MISCELLANEOUS RARE CAUSES OF NECK MASSES

Organized haematomas

AETIOLOGY

Blunt or penetrating trauma of the neck.

CLINICAL FEATURES

Patients present with a neck mass that usually causes local discomfort and occasionally constant pain.

DIAGNOSIS AND INVESTIGATIONS

A history of trauma is usually present although not always obvious. Ultrasound-guided FNAC will suggest diagnosis but the sonographic appearances depend on the age of the haematoma. If in the liquid state, blood can be aspirated. CT and MRI scanning will display distinct radiological features and determine the anatomical extent. Follow-up USS may be helpful to ensure there is no underlying lesion.

TREATMENT

Surgical excision is the treatment of choice although it may be difficult due to the surrounding fibrosis of the lesions.[91, 92]

Castleman disease

Castleman disease is a rare entity which is characterized by hyperplasia of lymph nodes and capillary proliferation that usually affects adolescents and young adults. Three histological patterns have been described: hyaline vascular type, plasma cell type and mixed type. Two clinical types have been identified; a localized type (ECL) usually of benign clinical course and a multicentric type (ECM) of worst prognosis as it may lead to the development of non-Hodgkin lymphoma.[93–95]

AETIOLOGY

It is unknown, although up to 50% of multicentric variants are caused by Kaposi sarcoma-associated virus (KSHV) a gamma herpes virus that causes KS and primary effusion lymphoma.

CLINICAL FEATURES

Patients usually present with a progressively enlarging lateral cervical lymphadenopathy often associated with an autoimmune iron-deficiency anaemia. ECM may present with B symptoms such as fever, anorexia and weight loss.

DIAGNOSIS AND INVESTIGATIONS

FBC shows iron-deficiency anaemia and the ESR is elevated. FNAC often shows a lymphocytic aspirate that is not normally diagnostic therefore surgical excision is advised for histological diagnosis. Imaging studies are often not useful.

TREATMENT

Anaemia is difficult to treat, as it does not often respond to iron supplements. Surgical excision is usually therapeutic in ECL although it may be difficult in ECM. Treatment with ganciclovir or the antiCD20 B-cell monoclonal antibody, may improve outcome in some patients with ECM. With ECM long-term follow-up is advised, in association with the haemato-oncology team.[93–95]

Kikuchi disease

Kikuchi disease (KD) is a self-limiting disease of lymph nodes that usually affects young women. It is also known as Kikuchi-Fujimoto disease and was first described by Kikuchi from Japan in 1972.[96, 97] Histologically, it is characterized by a histiocytic necrotizing lymphadenitis.

AETIOLOGY

The pathogenesis is unknown, however an autoimmune aetiology has been proposed as some human leucocyte antigen (HLA) class II genes, are more frequent in patients with KD. An association with systemic lupus erythematosus (SLE) has also been reported.

CLINICAL FEATURES

The disease often presents with persistent or intermittent fever as well as tender enlarged cervical lymph nodes. It is self-limiting but it may take up to 3 months to resolve.

DIAGNOSIS AND INVESTIGATIONS

The diagnosis can be confirmed by histopathological analysis of a lymph node following open biopsy.

TREATMENT

The disease is usually self-limiting and does not respond to antibiotic therapy. Supportive therapy with non-steroidal anti-inflammatory drugs may help to alleviate the lymphadenopathy, tenderness and pyrexia.[96, 97]

Kawasaki disease

Kawasaki disease (KWD) is an acute, self-limited vasculitis of childhood although it may also occur in adults. Tomisaku Kawasaki, from Japan, first described the condition in 1967.[98] In some countries, KWD has now surpassed acute rheumatic fever as the leading cause of acquired heart disease in children.

AETIOLOGY

The acute presentation and clustering of cases may indicate an infectious aetiology, however, the exact aetiology is unknown.

CLINICAL FEATURES

The illness is characterized by fever, bilateral non-exudative conjunctivitis, erythema of the lips and oral mucosa, changes in the extremities, rash, and cervical lymphadenopathy. Coronary artery aneurysms or ectasia develop in approximately 15–25% of untreated children and may lead to myocardial infarction and sudden death.[99, 100]

DIAGNOSIS AND INVESTIGATIONS

Diagnosis is based on the recognition of the characteristic sequence of clinical events, none of which are pathognomonic. Establishing the diagnosis may be further complicated by the occurrence of other, seemingly unrelated, clinical features, such as irritability, neck stiffness, sterile pyuria, pneumonitis and hepatitis. There is no laboratory test that can aid in confirming the diagnosis.

TREATMENT

Treatment is with intravenous gammaglobulin therapy and high doses of aspirin.[99, 100]

BOX 39.1 Other rare causes of cervical neck masses

- Sarcoidosis
- Fibromatosis colli
- Rosai–Dorfman disease
- Kimura's disease
- Dermatofibroma
- Prominent transverse process of atlas

KEY EVIDENCE

- This is a heterogeneous chapter addressing multiple benign disorders of the head and neck.
- There is lack of substantive high-level evidence due to the intrinsic nature of the disorders included. In most areas the evidence is at most level 2.
- Troublesome congenital abnormalities of the head and neck region are best treated with surgical excision whenever possible.
- Head and neck tuberculosis is where evidence is higher and should be treated with systemic antituberculous therapy with surgery having a limited role in its management.

KEY POINTS

- Benign disorders and masses of the neck represent a heterogenous group of diseases and its knowledge is imperative for the treating clinician.
- The evaluation and management of the patients presenting with neck lumps should be addressed with a clear systematic and uncompromising approach.
- All patients presenting with neck lumps should undergo ultrasound-guided fine needle aspiration whenever possible.
- The majority of congenital neck masses should be treated with meticulous surgical excision to avoid recurrence.
- Acquired non-inflammatory benign neck masses should be treated mainly with surgical excision to establish the histological diagnosis.
- Acquired inflammatory masses of the head and neck should be treated medically – with antibiotic therapy – and surgery is reserved for diagnosis – if this has not been established clinically or by FNAC – and for incision and drainage of established abscesses.
- Head and neck abscesses can be treated with repeated aspiration if indicated but incision and drainage should be always considered.

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CHAPTER 40

NECK SPACE INFECTIONS

James W. Moor

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SEARCH STRATEGY

Data in this chapter may be updated by a search of Pubmed and Medline using the keywords: deep neck spaces, deep neck space infection, deep neck infection and deep neck space infections.

INTRODUCTION

Neck space infections arise through a variety of aetiological processes and cause a diverse clinical picture. They carry the potential to cause life-threatening complications and death, although in the modern era with availability of broad-spectrum antibiotics, cross-sectional imaging and modern theatre facilities, the mortality rate is low. Nonetheless, appropriate and successful management requires a thorough understanding of the anatomy of the neck, knowledge of usual causative organisms and their sensitivities to commonly available antibiotics, clinical diagnostic skills and formulation of multi-speciality treatment plans with potential input from anaesthetists, microbiologists, oral and maxillofacial surgeons, otorhinolaryngologists, paediatricians and radiologists.

ANATOMICAL CONSIDERATIONS

The cervical fascia invests muscles and organs of the neck thereby limiting and influencing the direction of spread of infection. The relationship of the fascial layers to each other and adjacent structures creates potential spaces and therefore understanding the anatomy of the cervical fascia is key to understanding the anatomy of neck space infections.

The cervical fascia is divided into two layers: the superficial layer that envelops platysma and the muscles of facial expression and the deep layer, which, in turn, comprises superficial, middle and deep layers (**Figure 40.1**).

Superficial (or investing) layer of deep cervical fascia

This is attached superiorly to the superior nuchal line of the occipital bone, the mastoid process, the zygomatic arch, the inferior border of the mandible, the hyoid and the spinous processes of the cervical vertebrae. Inferiorly it is attached to the manubrium, the clavicle and the acromium and spine of the scapula. It forms the roof of the anterior and posterior triangles of the neck.

This layer forms the most superficial fascial boundary of the deep neck spaces and provides a robust barrier to the spread of infection, such that abscesses tend to track deep to it into adjacent, deeper neck spaces, or even into the mediastinum. It is not unusual for compression of deep structures to occur as a consequence of an accumulating abscess contained by the superficial layer of deep cervical fascia even to the extent that airway compromise becomes evident.[1]

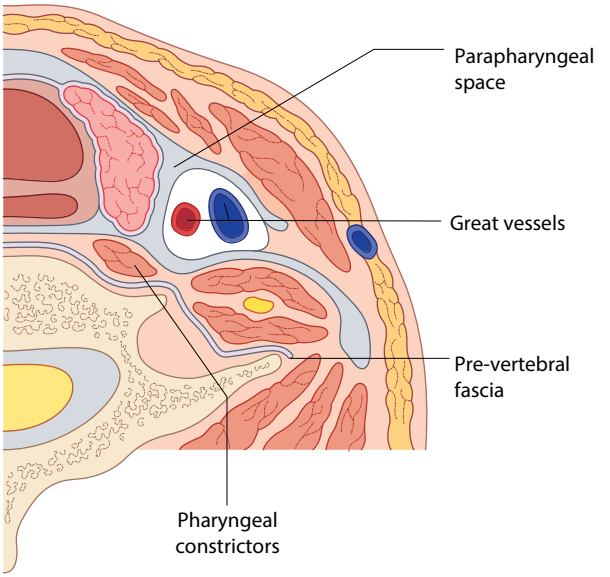

Figure 40.1 Axial section through C7 vertebrae detailing superficial cervical fascia, superficial, investing and deep layers of deep cervical fascia

Middle layer of deep cervical fascia (or pre-tracheal fascia)

This is limited to the anterior aspect of the neck; it splits to invest the thyroid gland, trachea and oesophagus and blends with the carotid fascia laterally. It descends into the superior mediastinum where it blends with the fibrous pericardium. Consequently, it bounds a deep space which extends from the neck into the mediastinum.

Deep layer of deep cervical fascia (prevertebral fascia)

The deep layer of deep cervical fascia (prevertebral fascia) forms part of a fascial sleeve for the prevertebral muscles that surround the vertebral column. It extends from the skull base to the third thoracic vertebra where it fuses with the anterior longitudinal ligament in the posterior mediastinum; it extends laterally as the axillary sheath.

Alar fascia

The alar fascia is a component of the deep layer of deep cervical fascia although it is described separately from it as it lies between the deep and middle layers of deep cervical fascia (**Figure 40.2**).[2]

NECK SPACES

Several deep neck spaces are classically described, created by the boundary layers of cervical fascia described above.

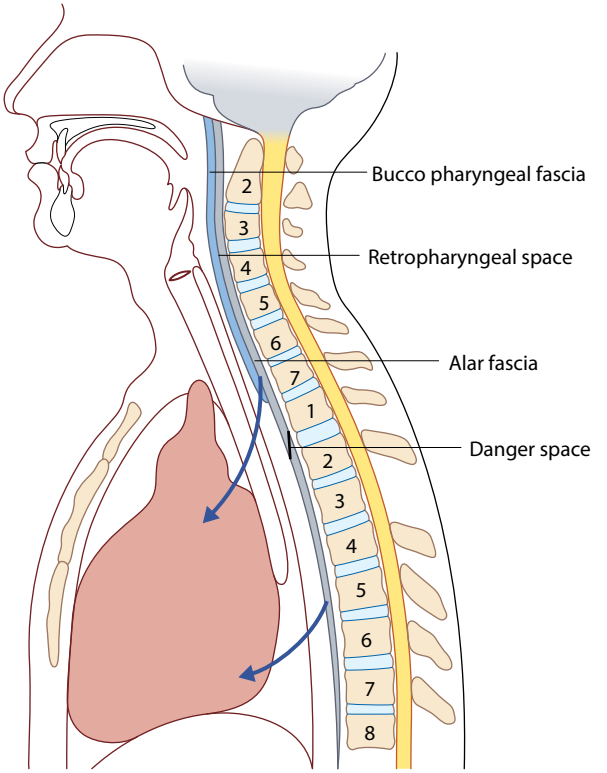

Figure 40.2 Sagittal section detailing retropharyngeal, prevertebral and 'danger spaces'.

Parapharyngeal space (lateral pharyngeal space, pharyngomaxillary space)

The parapharyngeal space (lateral pharyngeal space, pharyngomaxillary space) (**Figure 40.1**) forms an inverted cone with its base bounded by the petrous portion of the temporal bone and its apex at the level of the hyoid. It is crossed by the styloid process and attachments thus dividing the space into pre and post-styloid compartments. The pre-styloid compartment (anterior to the styloid complex) contains fat, connective tissue, the maxillary artery, the inferior alveolar nerve, the lingual nerve and the auriculotemporal nerve. In contrast, the post-styloid (posterior) compartment contains the carotid sheath and its contents, the glossopharyngeal and hypoglossal nerves, the sympathetic chain and associated lymph nodes.

Retropharyngeal space

The retropharyngeal space (**Figure 40.2**), contains lymph nodes and is bounded anteriorly by the middle layer of deep cervical fascia and posteriorly by the alar fascial component of the deep layer of deep cervical fascia. It extends craniocaudally from the skull base to the tracheal bifurcation. A midline raphe is formed by the attachment of the superior constrictor muscles to the alar fascia.

So-called 'danger space'

The so-called 'danger space' is a potential space between the alar fascia anteriorly and the deep layer of deep cervical fascia (prevertebral fascia) posteriorly, which extends craniocaudally from the skull base to the diaphragm.

Submandibular space

The submandibular space (**Figures 40.4, 40.5** and **40.6**), is bounded by the floor of mouth mucosa cranially and the mandible laterally, whilst the anterior and posterior bellies of the digastric muscle form the anteroinferior and posteroinferior boundaries respectively. The mylohyoid muscle lies anteriorly and the stylomandibular ligament posteriorly. The space is divided by the mylohyoid muscle into sublingual and submandibular compartments which contain the sublingual salivary gland and lymph nodes respectively. These compartments are continuous around the posterior free edge of the mylohyoid muscle and the submandibular gland lies within both as it straddles this free edge.

Masticator space

The masticator space, (**Figures 40.7** and **40.8**), lies inferior to the skull base (greater wing of sphenoid and squamous temporal bone) and is bounded by the pharyngeal mucosa medially and the medial surface of the ramus of the mandible laterally. The lateral pterygoid plate, superior constrictor, tensor and levator palatini muscles constitute the posteromedial border and can be subdivided into superficial temporal space superolaterally, deep temporal space superomedially, pterygoid space inferomedially and masseteric space inferolaterally. Communication with the pterygopalatine fossa exists via the pterygomaxillary fissure; the muscles of mastication and the mandibular division of the trigeminal nerve are contained within it.

Visceral space

The visceral space is formed anteriorly by the middle layer of deep cervical fascia that envelops the thyroid and the trachea, and posteriorly by the deep layer of deep cervical fascia. It contains the larynx, hypopharynx, cervical oesophagus, proximal trachea, thyroid and parathyroid glands.

Carotid space

The carotid space is a potential space formed by the carotid sheath, which is in itself formed from all three layers of deep cervical fascia blending together. It contains the common carotid artery, the internal jugular vein (IJV) and the vagus nerve.

Parotid space

The parotid space (**Figure 40.9**), is formed by the superficial layer of deep cervical fascia that splits to invest the parotid gland and therefore also contains the facial nerve, the retromandibular vein, the external carotid artery and its terminal branches.

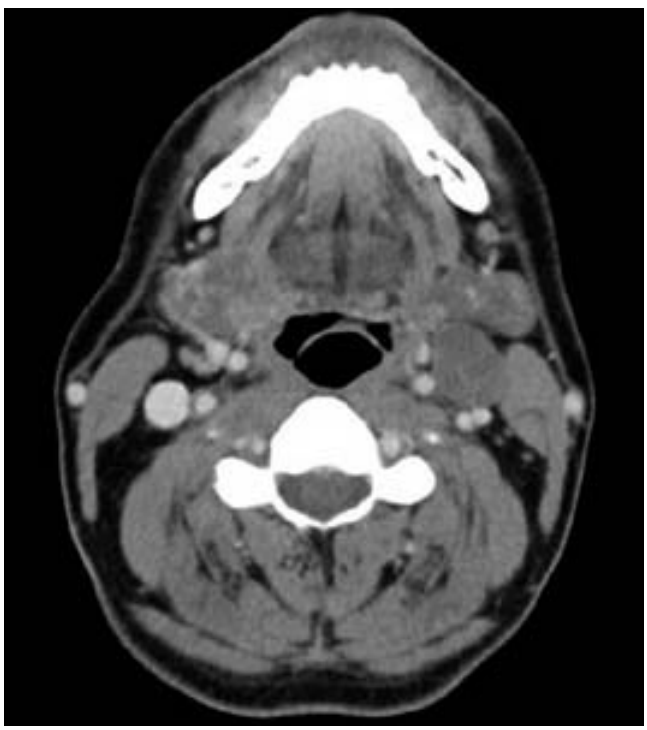

Figure 40.3 Axial contrast-enhanced CT scan demonstrating lymph node abscess in left parapharyngeal space. Note posterior displacement of internal jugular vein and medialization of carotid vessels. Mass effect and mucosal oedema cause subtle asymmetry of the airway at the level of the epiglottis.

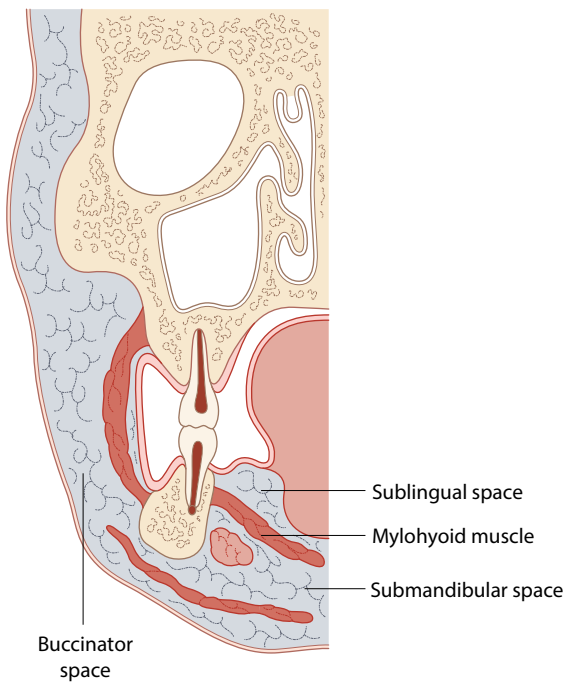

Figure 40.4 Submandibular, sublingual and buccinator spaces.

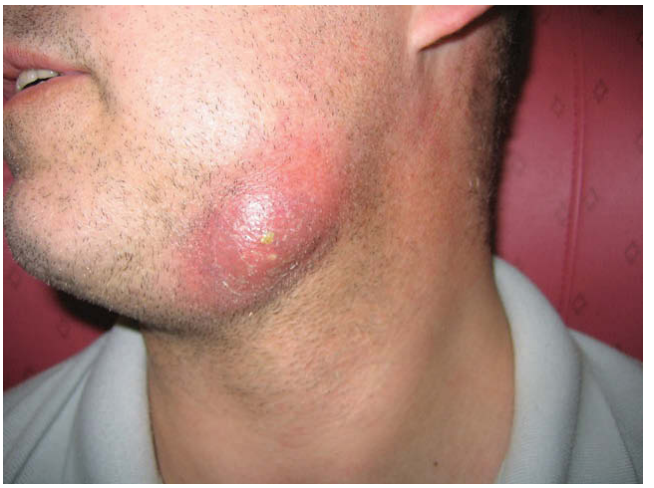

Figure 40.5 Pointing abscess of the submandibular space.

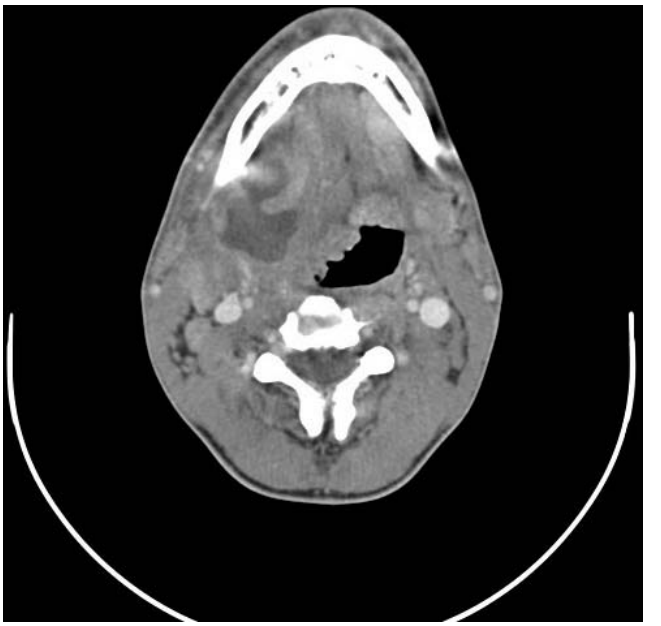

Figure 40.6 Axial contrast-enhanced CT scan showing abscess in the right submandibular space (different patient to Figure 40.5). A large hypodense area medial to the mandible is evident with ring enhancement and oedema affecting the soft tissues superficial and deep to the abscess. The pharyngeal lumen is narrowed and shifted to the contralateral side.

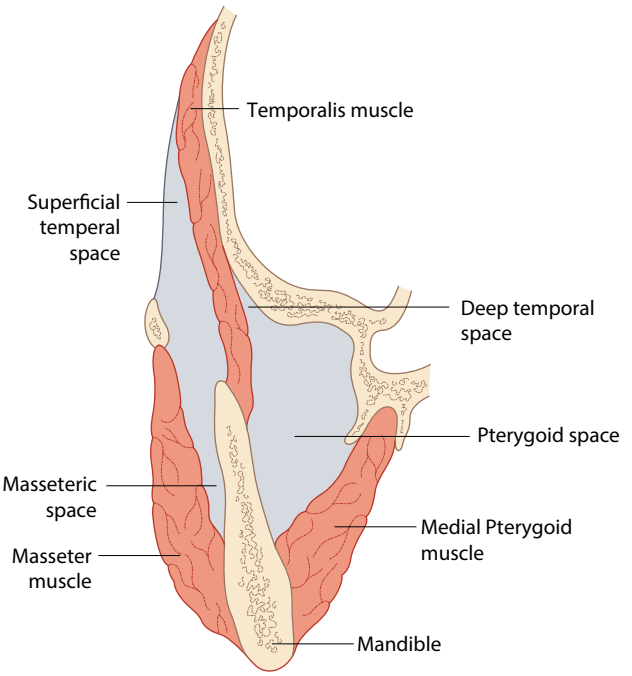

Figure 40.7 The masticator space and subdivisions.

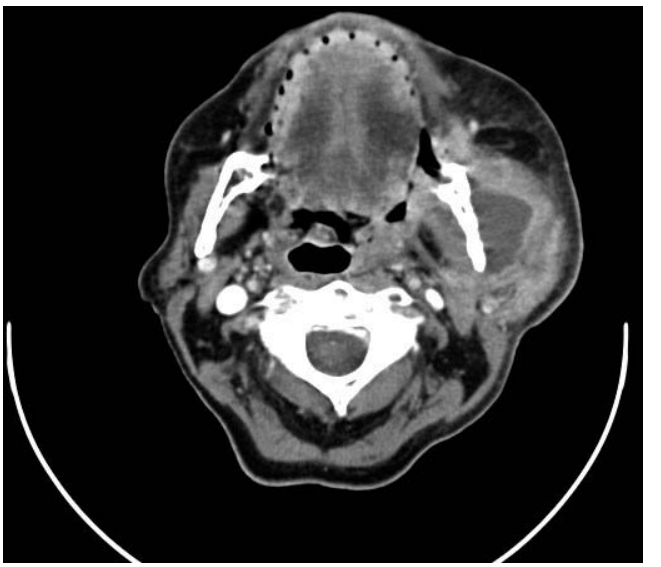

Figure 40.8 Axial contrast-enhanced CT scan showing masseteric space and pterygoid space abscess. Ring enhancement is evident around the hypodense abscess cavity as well as gross soft tissue oedema superficial and deep to the abscess causing asymmetry of the appearance of the external neck and deviation of the pharyngeal lumen contralaterally.

Peritonsillar space

The peritonsillar space lies lateral to the pharyngeal tonsil and medial to the superior constrictor muscle. It contains loose connective tissue and is the site of accumulation of pus in peritonsillar abscess, or quinsy.

It is important to note that direct communication exists between the posterior aspect of the parapharyngeal space and the retropharyngeal space, as well as the anterior parapharyngeal space and the submandibular space. Moreover, peritonsillar space abscess can directly spread to the parapharyngeal space by direct extension, via lymph and/or blood vessels which traverse the superior constrictor muscle.[1–3]

AETIOLOGY

In the pre-antibiotic era, 70% of deep neck space infections (DNSI) were caused by pharyngotonsillitis and 20% by odontogenic infection.[4] Recent published data

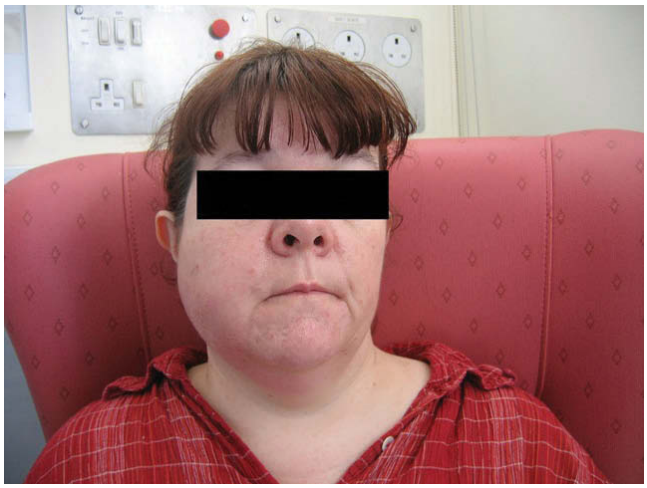

Figure 40.9 Parotid space abscess.

demonstrate that odontogenic infection is now the most common aetiological factor causing 31–49% of DNSIs.[5, 6] Peritonsillitis is variably mentioned as the underlying cause in approximately 7–20% of cases[4, 7] whilst in 17–57% of cases the primary source of infection is not clinically apparent.[7, 8]

Retrospective case series which include large numbers of cases describe various aetiological factors including ingestion of foreign body, coexisting Diabetes Mellitus (DM), Human Immunodeficiency Virus (HIV) infection and intravenous (IV) drug abuse although it is notable that the patient demographics from which these series have drawn their cases show considerable baseline variability and it would be inappropriate to extrapolate these findings to groups outwith the study populations. It is worth mentioning other cause of DNSI that have been reported and include mycobacterial infection, mandibular fracture, sialolithiasis, parotitis and thyroid infection.[4, 5, 7, 8]

INCIDENCE

The true incidence of DNSI is unknown. According to Hospital Episode Statistics (HES) data in England during the 12 months to the year ending March 2016 it is recorded that there were 216 admissions for 'drainage of retropharyngeal abscess'. By comparison there were 5246 admissions for 'drainage of abscess of peritonsillar region' during the same period. Other neck space infections are not coded in the data presented.[9]

CLINICAL FEATURES

Pain is the pre-eminent symptom in most patients, and in some published series it is almost ubiquitous.[7] Pain is usually focused at the neck space harbouring the infection, but can also be referred to the ear, cause odynophagia, trismus or torticollis. Other symptoms caused will depend on the site of infection but include dysphonia, dysphagia, sialorrhoea or cough.

The most common clinical signs include swelling in the neck, pyrexia and trismus. Skin fistulae, medial or anterior displacement of the lateral or posterior pharyngeal wall and gingival swelling occur commonly but less frequently.[5, 7, 10, 11]

Most series,[4, 5, 8, 13–16] although not all,[7, 11] demonstrate that males are more commonly affected than females by a ratio of approximately 1.6:1. The majority of patients, male and female, occupy the 20–40 year age range, with an estimated median age in the mid-30s. However, the age range of affected patients is wide and all age groups can be affected. The reasons why patients in their 3rd – 5th decades show the highest incidence of disease, and, why males are more commonly affected is not known. Co existent diseases (see 'Aetiology' above) include dental caries, DM, IV drug abuse and HIV infection.

CLINICAL ASSESSMENT AND INVESTIGATIONS

Assessment begins by taking a full clinical history and performing a thorough examination including fibre-optic nasendoscopy to assess the upper aerodigestive tract mucosa and airway patency simultaneously. Relevant clinical findings will lead the attending clinician to the differential diagnosis and will influence the subsequent lines of enquiry and early / emergent management strategy. Due to the potential for DNSIs to cause significant airway compromise it is essential that the initial assessment of patients is performed with high priority consideration as to whether the patient requires emergency airway management (see 'Airway management' below) or whether the patient is capable of maintaining their own airway for the foreseeable future. This initial assessment is important as it determines whether cross-sectional imaging with the patient in a supine position is safe to undertake. Consequently, it is essential that initial assessment is undertaken by clinicians experienced in the management of patients with airway compromise and who have the necessary clinical skills to be able to achieve a secure airway in the event of sudden deterioration.

When either the airway is secured or it is considered that significant airway compromise is not imminent, then cross-sectional radiological assessment can be undertaken in the form of contrast-enhanced CT as this is considered to be the gold-standard imaging modality.[17, 18] Due to potential communication of the visceral, retropharyngeal, danger and prevertebral spaces with the mediastinum it is imperative to include the mediastinum in the CT scan field. Where there is clinical concern of septic emboli spreading to the brain, lungs or liver these organs are required to be imaged also. Abscesses will demonstrate characteristic rim enhancement on CT imaging and cellulitis may be represented by fluid and fat stranding in the subcutaneous tissues and along fascial planes, whilst

myositis is suggested by enlargement and hyperenhancement of the adjacent musculature. Ultrasound imaging, in contrast, may be helpful to determine whether an abscess has sufficiently liquified to be drained, and may also be useful in targeting attempted drainage.[18] Where the infection is considered to be of dental origin an orthopantomogram is acquired, as it is in the case of infection of unknown aetiology.

Regular observations including pulse rate, blood pressure, temperature and respiratory rate are mandatory – the frequency of such observation being determined by the clinical condition of the patient. Blood is sent for urea, creatinine and electrolytes assays, blood count, including differential white cell count, C-reactive protein and erythrocyte sedimentation rate. Consideration is given as to whether it is appropriate to send blood for microbial culture. Pustulating skin fistulae and obviously infected dental sockets or roots may be swabbed for microbial cultures but routine pharyngeal microbiology swabs **must not** be taken to avoid precipitating an airway crisis as a consequence of triggering the gag reflex. If the clinical condition of the patient dictates it, appropriate venous access should be secured. Finally, it is essential that the patient is managed in a clinical environment commensurate with the severity of their presenting clinical condition.

SPECIFIC NECK SPACE INFECTIONS

- **Ludwig's angina** is considered to be an acute infection of bilateral sublingual and submandibular spaces, and the submental space. It occurs most commonly as a consequence of anterior dental infection.[1] In these patients, as a consequence of the underlying abscess, there is typically gross oedema of the floor of mouth and of the anterior tongue, such that the tongue becomes grossly swollen, protuberant and immobile. The result is significant risk of life-threatening airway obstruction and decision-making with regard to airway management needs to include emergency tracheostomy as a primary treatment option.
- **The parapharyngeal space (PPS), Figures 40.1** and **40.3**, can become infected either primarily or as a consequence of direct spread of infection from the submandibular and/ or the retropharyngeal spaces. A recent study of DNSIs of this space in particular demonstrated different clinical features depending on whether the anterior or posterior parapharyngeal space (APPS and PPPS respectively) is infected. The difference arises due to the anatomical contents of these sub-spaces. The APPS contains fat which in the presence of infection may liquefy, develop into pus and hence abscess formation. The PPPS is rich in lymph nodes and vessels and it is suggested that infection in this space causes lymphadenitis, but is less likely to develop into abscess formation. Consequently, APPS and PPPS infections can have different clinical courses and be managed differently, with a more conservative approach possible in PPPS and aggressive surgical drainage of pus required for APPS.[11] However, the ultimate distinction between the two is made on imaging.
- **Suppurative thyroiditis** – This usually occurs due to abnormal development of the 4th branchial pouch, resulting in a communicating sinus between the pharynx and the thyroid bed; in some cases, a proximal orifice may be identified as a defect in the mucosa of the piriform fossa. Patients with episodic recurrent suppurative thyroiditis need to have this diagnosis considered. Barium swallow examination and/ or cross-sectional imaging with contrast-enhanced CT or MRI may demonstrate the sinus tract, and the orifice will usually be identifiable by careful inspection of the piriform fossa mucosa under anaesthetic using direct pharyngoscopy. There is a preponderance for these affecting the left side of the hypopharynx. Treatment consists of excision of the tract of the sinus including the ipsilateral hemithyroid, although care must be taken to accurately identify the relationship of the sinus to the recurrent laryngeal nerve, as this can be variable.[19, 20] Alternatively, obliteration of the sinus opening in the hypopharynx using monopolar diathermy has been reported to be effective at preventing further infections.[21]
- **Retropharyngeal space abscess** is usually caused in adults by penetrating trauma through the posterior mucosal wall of the pharynx or cervical oesophagus. However, in children it is more commonly secondary to suppuration of retropharyngeal lymph nodes following an upper respiratory tract infection, although retropharyngeal lymph nodes tend to regress after the age of 5 years. Retropharyngeal space abscess is a significant cause of airway compromise, and as a consequence surgical tracheostomy is not uncommonly required.[22, 23] An attempt to intubate the patient using an endotracheal tube by an unprepared anaesthetist may lead to traumatic rupture of the abscess due to pressure from the tip of the intubating laryngoscope and subsequent flooding of the unprotected airway with pus and blood. Once the airway has been appropriately secured the abscess can be drained in a controlled fashion, the incision is made at the most inferior aspect of the collection such that further accumulation of pus will drain through gravity into the pharynx.
- **Masticator space infection** (**Figure 40.9**), usually arises secondary to odontogenic infection or less commonly as spread from infection in the parotid space, submandibular space or peritonsillar space. Trismus is a common clinical finding due to oedema of the adjacent pterygoid muscles.

MICROBIOLOGY AND PHARMACOLOGY

A wide range of aerobic, microaerophilic and anaerobic microorganisms typically colonize neck space infections.[24]

The predominant organism responsible for a given DNSI is influenced by the prime aetiological factor, be it odontogenic infection, penetrating neck trauma, IV drug use etc. The prevalence of these factors may depend on the geography, socio-economic status, and the incidence of predisposing factors such as coexisting DM and HIV infection.

However, there are some similarities reported in the literature with regards to microbiology of DNSIs as *Peptostreptococcus* spp., Viridans Group Streptococci, *Staphylococcus aureus*, *Staphylococcus epidermidis* and *Klebsiella pneumoniae* are commonly present in many reported series.

Typically, broad-spectrum antibiotics are commenced prior to receipt of microbiological results, and in cases of a conservatively managed patient there may be no microbiological input into the case at all. Indeed, even with adequate pus sampling, failure to culture the causative bacteria occurs in approximately 25% of cases, which may be due to the difficulties in culturing anaerobic organisms that are inherently fastidious, or liberal use of antibiotics prior to referral to secondary care facilities.[8] Polymicrobial cultures are commonly seen.[25]

Antibiotic treatment should reflect the diverse nature of the microbiology of the condition, the likely aetiology and consider the possibility of adverse reactions in patients receiving treatment. Broad-spectrum antibiotics are prescribed, either amoxicillin/clavulanate, or 2nd or 3rd generation cephalosporins with metronidazole.[26] Antibiotic prescriptions need to be reviewed in the light of culture results and changed as necessary. Clindamycin and vancomycin are commonly used second-line agents, or potential first-line agents when drug allergy or sensitivity restrict choice. Resistance to antimicrobial agents is rising as evidenced by reported resistance to clindamycin in 11–18%, erythromycin 14%, penicillins 7–8% and aminopenicillins 0–3%[26] of cases.

SURGICAL TREATMENT

The maxim that one should '...never let the sun set on an undrained abscess' has guided management of neck space abscesses for many years especially in an era that predated cross-sectional imaging. Changes in radiological assessment have moved away from plain soft-tissue neck X-rays and now utilize contrast-enhanced rapid acquisition spiral tomographic scanners that permit reconstruction of acquired images in multiple planes and three dimensions. There has consequently been a considerable increase in the sensitivity and specificity of abscess diagnoses on radiological grounds, and with it the opportunity for a more conservative approach to management of selected cases.

Nonetheless, neck space infection is a potentially life-threatening infection; crude mortality rates of up to 2% have been published. The primary responsibility of the treating clinician is to ensure protection of the airway and to consider surgical drainage of pus secondarily. However, not all neck space infections develop into abscesses and even in the presence of an imaging study diagnostic of a small deep-seated abscess there has been a trend towards conservative management ***wherever possible.***[7]

Most published series report the surgical intervention rate, with the reported median confirming that approximately 80% of patients underwent surgical drainage of an abscess – although the range of reported intervention between studies is wide (10–100%)[5, 7, 8, 10, 13, 16, 27] and probably reflects preferred local practice rather than anything else. Usually, in cases without impending airway compromise, surgical intervention follows a period of conservative management of 24–48 hours with a decision taken to surgically intervene if there is a clinical failure to respond (persistent pyrexia, persisting or worsening pain, etc).

If surgical treatment is deemed necessary various treatment options exist. Conventional surgical drainage procedures incise the skin over the area of maximal fluctuance or induration. Following evacuation of the abscess contents, the abscess wall is curetted, and any loculations or boundaries between adjacent and communicating neck spaces (e.g. retropharyngeal, parapharyngeal and submandibular) are broken down – often with digital dissection. In classical Ludwig`s angina it is often necessary to undertake this procedure through multiple transcutaneous stab incisions to ensure that adequate drainage of these spaces bilaterally is achieved. Drains are secured to permit further drainage of pus; it is the author's preference to use soft, non-suction drains that protrude through the incised wound into the abscess cavity, with simple dry gauze dressings adhered distally. The activity of the drain is recorded by the number of dressing changes per 24 hours and they are removed gradually over a period of days. In the case of odontogenic infections the underlying dental infection(s) should be dealt with during the same general anaesthetic.

Consideration has been made of the merits of ultrasound-guided aspiration of pus compared to open surgical drainage and a small prospective randomized trial reported a shorter length of hospital stay (reduced mean length of hospital stay from 5.2 to 3.1 days), a 41% cost reduction and no difference in treatment efficacy or complication rate in the ultrasound aspiration group.[28] Also, microbiology sampling by aspiration rather than by microbiological swabs of an incised abscess has been shown to increase the isolation of anaerobes and reduce the detection of potential skin contaminants.[24, 28, 29]

AIRWAY MANAGEMENT

Maintaining a patent and safe airway is the pre-eminent step in management of patients with DNSI. Mortality can occur as a consequence of asphyxiation and hypoxia as well as delayed septic complications. The widespread use of antibiotics has reduced the morbidity and mortality from pharyngeal oedema and permits a watch and wait policy in selected cases. Conversely, large abscesses causing a precarious airway demand a coherent management

strategy to secure the airway prior to surgical drainage and to maintain the airway post-operatively. The decision as to which management strategy can be adopted is made on a case-by-case basis.

Conventional endotracheal intubation is not always possible due to trismus, reduced neck extension, laryngopharyngeal oedema, mass effect from the abscess and the friable nature of the mucosa that readily obstructs the view due to contact bleeding. It is of utmost importance that induction of anaesthesia does not lead to a situation where neither ventilation nor intubation by conventional means are possible. Algorithms are available online[32] to assist joint anaesthetic/surgical airway management and these should be agreed by the attending teams prior to commencement of any procedure.

Options available to manage the airway are numerous and described elsewhere (see Chapter 72, Upper airway obstruction and tracheostomy).[12, 33] Patients that have impending airway obstruction need to be transferred to a place of safety for airway management. In the UK, this would be to one of the anaesthetic rooms in a hospital operating theatre complex with anaesthetic and surgical staff who have the appropriate experience in attendance. Once a plan of action has been agreed, the surgical and scrub teams prepare the operating theatre in anticipation of the requirement for an emergency tracheostomy in the event of failed intubation and loss of airway. If it is deemed that the patient will tolerate it, it is advisable to infiltrate 2% lignocaine with 1:80000 adrenaline solution into the skin at the site of potential tracheostomy prior to the commencement of the anaesthetic procedure. In the event of an emergency tracheostomy being required, this step does not need to be repeated; the adrenalin will have caused some local vasoconstriction and it lessens the likelihood of flexion/extension reaction from a semi-obtunded patient resultant from the pain of the skin incision.

If there are sufficient concerns that oral or nasal intubation are unlikely to be successful, it is preferable to perform tracheostomy under local anaesthetic as an emergency (as opposed to an emergency 'crash' tracheostomy).

Once the airway has been secured, the abscess can be drained in a controlled fashion as described.

COMPLICATIONS

The incidence of resulting complications reported varies considerably between different published series. Tracheostomy, either planned or 'crash', is reported as necessary in 3–22% of patients[4, 7] and, in general, patients with Ludwig's and retropharyngeal abscess are at higher risk of airway obstruction than those presenting with lateralized abscesses. Other complications include pneumonia, IJV thrombosis, carotid artery aneurysm and rupture, necrotizing fasciitis, skin fistulae and defects, vocal cord and facial palsies, descending mediastinitis, upper gastrointestinal bleeding, iatrogenic bleeding following tracheostomy insertion, septic emboli from IJV thrombosis, sepsis, multi-organ failure and death.

Patients with pre-existing comorbidities are more likely to suffer from complications, as are patients that have infection in more than two neck spaces: in the series published by Kang et al,[34] abscess formation in the retropharyngeal space was always seen in patients that developed mediastinitis. A combined thoracic and cervical exploration may be required to facilitate adequate treatment in those patients.

PAEDIATRIC NECK SPACE INFECTION

It has been reported that neck space infection in children is increasing in incidence[22, 35] although it is not known why. Childhood neck space infection more often results from an upper respiratory tract infection than from odontogenic aetiologies and methicillin-resistant *Staphylococcus aureus* (MRSA) is more frequently isolated from pus samples taken from DNSIs in children than in adults. Two published series have reported positive MRSA cultures in 27% and 42% of cases.[36, 37] There is a rising prevalence in cultures positive for MRSA demonstrated year on year in many other series.[36–40]

The management principles for paediatric DNSI are no different to those required to treat adults; maintenance of the airway is of the utmost importance, appropriate imaging to identify the distribution of affected neck spaces, treatment with broad-spectrum antibiotics until specific sensitivities are known, and a decision made and then frequently reviewed as to whether surgical drainage is indicated, and if so, what form that surgical procedure takes.

Paediatric patients demonstrate different physiological responses to sepsis in comparison to adults and attending clinicians need to understand and respond to alterations in the clinical condition of paediatric patients with rapidity in order to avoid catastrophic deterioration of the airway and/or the cardiovascular system from impending septic shock.

CONCLUSION

Neck space infections are seen in patients of all ages, with and without pre-existing comorbid problems. Assessment and management of the airway is required alongside treatment of the underlying infection with broad-spectrum antibiotics. Life-threatening complications occur frequently which, given the anatomy of the cervical fascia, may be distant to the primary focus of infection. However, mortality is usually an infrequent occurrence with appropriate and timely treatment.

FUTURE RESEARCH

- Ongoing publication of prospectively collated microbiology data pertaining to DNSI to assess changing trends in causative organisms and patterns of antibiotic resistance, ideally across different continents.
- Safety and efficacy of conservative vs. US-guided aspiration vs. surgical management of DNSI in children with small localized abscesses.
- How is the incidence and management of DNSI being influenced by rising incidences of diabetes and obesity?

KEY POINTS

- Understanding of the anatomy of cervical fascial planes is key to diagnosis and management.
- Cross-sectional imaging, where possible, will provide extremely useful information to aid treatment decision-making.
- Generally the mantra 'Never let the sun set on undrained pus' should be adhered to. But, some non-toxic patients with small localized abscesses may be suitable for more conservative management. These patients require very close clinical observation and regular review of their treatment plan in the light of a changing clinical situation.

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CHAPTER 41

ANATOMY AND EMBRYOLOGY OF THE MOUTH AND DENTITION

Barry K.B. Berkovitz

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SEARCH STRATEGY

Data in this chapter may be updated by a search using the following keywords: mouth, dentition, anatomy and embryology.

INTRODUCTION

The importance of the mouth to the otolaryngologist is self-evident. It is the portal of entry for visual examination of the oropharynx, larynx and the opening of the Eustachian tube in the nasopharynx. It is also the portal of entry for many of the surgical procedures undertaken in these regions. Malformations in the mouth, such as cleft palate, may have important consequences for the healthy functioning of the system. Infection or tumours from the mouth may spread to involve the ear, nose and throat. As an example, infection from maxillary teeth may give referred pain to the nasal region, while infection from mandibular teeth may spread to the neck and result in severe (and sometimes fatal) respiratory embarrassment. Due to its close physical (and also evolutionary) relationship to the ear, clinical conditions affecting the jaw joint (temporomandibular joint) may need to be differentiated from those directly involving the ear.

The mouth can be subdivided into the vestibule (external to the teeth) and the oral cavity proper (internal to the teeth). The mouth extends from the lips and cheeks externally to the anterior pillars of the fauces (palatoglossal arches) internally, where it continues into the oropharynx. The roof of the mouth is the palate and separates the oral and nasal cavities. The floor of the mouth is formed by the mylohyoid muscles and is occupied mainly by the tongue. The lateral walls of the mouth are defined by the cheeks and retromolar regions. Opening into the mouth are three pairs of major salivary glands (parotid, submandibular and sublingual) and numerous minor salivary glands (labial, buccal, palatal, lingual).

PALATE

The palate is divisible into two regions: the hard palate in front and soft palate behind.

Hard palate

The skeleton of the hard palate is formed by the palatine processes of the maxillae and the horizontal plates of the palatine bones. The oral mucosa is bound tightly to the underlying periosteum. In its more lateral regions it also possesses a submucosa where the main neurovascular bundles lie (**Figure 41.1**).

The periphery of the hard palate surrounding the necks of the teeth is termed the gingiva and a zone similarly lacking submucosa runs anteroposteriorly in the midline as a narrow, low ridge; the palatine raphe. At the anterior

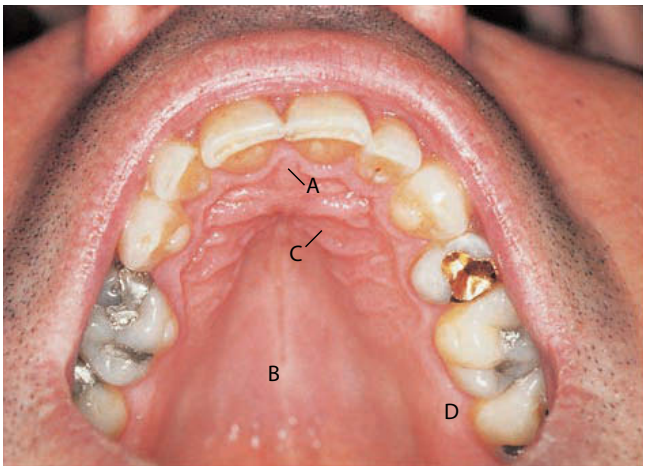

Figure 41.1 The hard palate. A, Incisive papilla; B, palatine raphe; C, palatine rugae; D, alveolus. Reprinted from Ref. 1 by permission from Elsevier.

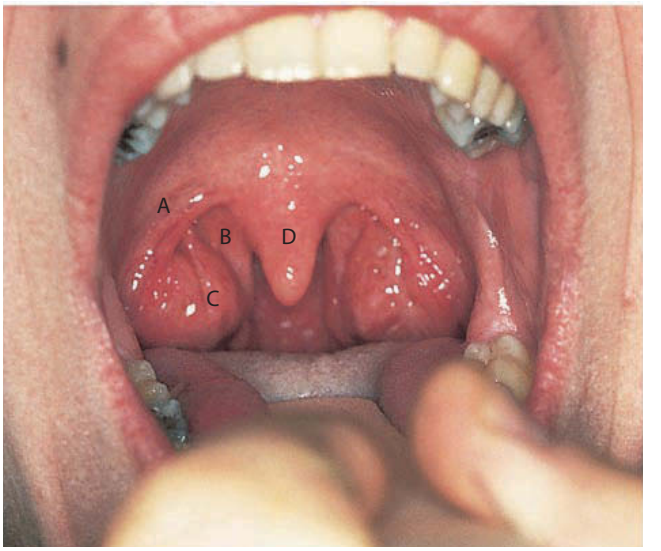

Figure 41.2 The soft palate and oropharyngeal isthmus. A, Palatoglossal fold; B, palatopharyngeal fold; C, palatine tonsil; D, uvula. Reprinted from Ref. 1 by permission from Elsevier.

extremity of the raphe behind the incisor teeth is a small prominence, the incisive papilla that covers the incisive fossa at the oral opening of the incisive canal. Radiating outwards from the palatine raphe in the anterior half of the hard palate are irregular transverse ridges or rugae. The pattern of rugae is unique for the individual and has been used in forensic science to identify a dead individual.

The submucosa in the posterior half of the hard palate contains minor mucous salivary glands. These secrete through numerous small ducts although, bilaterally, larger ducts collecting from many of these glands often open at the paired palatine foveae. These are two sagittally elongated depressions, sometimes a few millimetres deep, which flank the midline raphe at the posterior border of the hard palate.

The upper nasal surface of the hard palate is the floor of the nasal cavity and is covered by ciliated respiratory epithelium. The lower oral masticatory surface is covered by keratinized epithelium.

Soft palate

The soft palate is a mobile flap suspended from the back of the hard palate, sloping down between the oral and nasal parts of the pharynx (**Figure 41.2**). The boundary between the hard and soft palate may be distinguished by a change in colour, the soft palate being a darker red with a yellowish tint. In its relaxed and pendant position, its anterior (oral) surface is concave, with a median raphe. Its posterior aspect is convex and continuous with the nasal floor. A median conical process, the uvula, projects downwards from its posterior border. Just behind and medial to each upper alveolar process, in the lateral region of the anterior part of the soft palate, a small bony prominence can be felt. This is produced by the pterygoid hamulus, an extension of the medial pterygoid plate of the sphenoid bone.

The soft palate contains an aponeurosis, muscular tissue, vessels, nerves, lymphoid tissue and mucous glands, while some taste buds are situated on its oral aspect.

A thin, fibrous palatine aponeurosis is attached to the posterior border of the hard palate. It represents the expanded tendons of the tensor veli palatini muscles and provides the fibrous skeleton of the soft palate that supports the palatine musculature. The aponeurosis is thick in the anterior two-thirds of the soft palate but very thin further back. The palatine muscles are attached to the aponeurosis.

CHEEKS

The cheeks are covered externally by skin and internally by mucous membrane (buccal mucosa) and have a muscular skeleton, the buccinator. Internally, the pink mucosa of the cheek adheres firmly to the buccinator muscle. Few structural landmarks are visible. The parotid duct drains in the region of a small parotid papilla opposite the maxillary second molar tooth. A whitish line (the linea alba) may be seen at a position related to the occlusal plane of the teeth: this hyperkeratinized line is presumably the result of continuous mild trauma during biting. Yellow patches (Fordyce's spots) representing ectopic sebaceous glands may be evident on the internal surface of the cheek. Their numbers increase in puberty and in later life. Behind the molar teeth, a fold of mucosa can be seen extending from the upper to the lower alveolus, especially when the mouth is opened widely. This fold covers the pterygomandibular raphe that extends from the pterygoid hamulus to the back of the mylohyoid line. The raphe gives origin to the buccinator muscle from its anterior surface and the superior constrictor muscle from its posterior surface. The entrance to the pterygomandibular space lies lateral to the pterygomandibular raphe and medial to the ridge produced by the anterior border of the ramus of the mandible.

Between the lips or cheeks and the teeth lies a slit-like space, the oral vestibule. Where the mucosa covering

the alveolus of the jaw is reflected onto the lips and cheeks, a trough or sulcus is formed which is called the fornix vestibuli. With the teeth in occlusion, a space still exists behind the last molar tooth (retromolar region), allowing for the passage of fluids when the jaws are wired together following fractures. A variable number of sickle-shaped folds containing loose connective tissue run across the fornix vestibuli. The upper and lower labial frena (or frenula) are constant folds in the midline. Other folds may traverse the fornix near the canines or premolars.

LIPS

Like the cheeks, the lips are covered externally by skin and internally by mucous membrane (labial mucosa) that is smooth and shiny and shows small elevations caused by underlying mucous glands. The lips have a muscular skeleton, the orbicularis oris muscle.

The red zone of the lip (the vermilion) is a feature characteristic of man. In the upper lip, the vermilion protrudes externally in the midline to form the tubercle, above which is situated a grooved region termed the philtrum. The lower lip shows a slight depression corresponding to the tubercle.

FLOOR OF THE MOUTH

This comprises a small horseshoe-shaped region beneath the tongue (**Figure 41.3**). Near the base of the tongue in the midline, a fold of tissue called the lingual frenum is seen to extend onto the inferior surface of the tongue. The sublingual papilla is a conspicuous centrally positioned protuberance at the base of the tongue. The submandibular salivary ducts open into the mouth at this papilla. On either side of the sublingual papilla are the sublingual folds, beneath which lie the submandibular ducts and sublingual salivary glands. The muscle forming the floor of the mouth is the mylohyoid muscle.

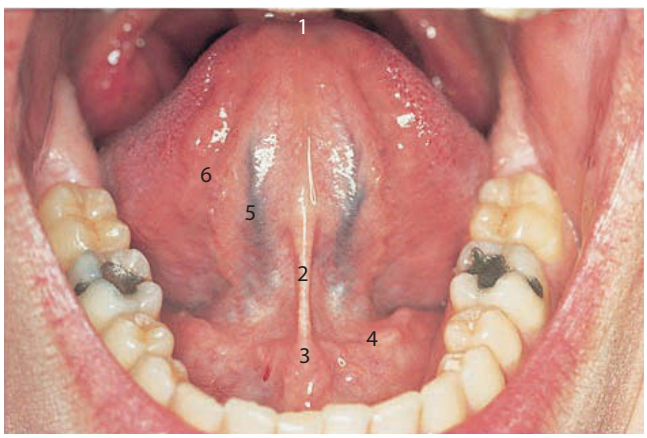

Figure 41.3 The ventral surface of the tongue, related to the floor of the mouth. 1, Tip of tongue; 2, lingual frenum; 3, sublingual papilla; 4, sublingual fold; 5, deep lingual vein; 6, fimbriated fold. Reprinted from Ref. 1 by permission from Elsevier.

OROPHARYNX

The oropharynx extends from the soft palate to the upper border of the epiglottis (see **Figure 41.2**). Its lateral wall consists of the palatopharyngeal arch, with the palatine tonsil lying between this arch and the palatoglossal arch anteriorly. The two arches are also known as the pillars of the fauces. The floor of the oropharynx is occupied by the pharyngeal aspect of the tongue.

The aperture of communication between the mouth and pharynx, the oropharyngeal isthmus, is situated between the soft palate above and the dorsum of the tongue below, bounded on both sides by the palatoglossal arches. Each palatoglossal arch runs downwards, laterally and forwards and contains the palatoglossus muscle with its covering mucous membrane. The approximation of the arches, to shut off the mouth from the oropharynx, is essential to deglutition.

Palatine tonsil

The palatine tonsil is a mass of lymphoid tissue situated in the lateral wall of the oropharynx, where it lies within the tonsillar fossa between the diverging palatopharyngeal and palatoglossal arches. It forms the anteroinferior part of Waldeyer's ring of lymphoid tissue. This ring surrounds the openings into the digestive and respiratory tracts and consists of the palatine and tubal tonsils laterally, the nasopharyngeal tonsil (adenoids) and smaller collections of lymphoid tissue in the intertonsillar intervals posterosuperiorly, and the lingual tonsil inferiorly.

The medial (free) surface of the palatine tonsil projects into the oropharynx and usually presents a pitted appearance. These pits, 10–15 in number, lead into a system of blind-ending, often highly branching crypts, which extend through the whole thickness of the tonsil. The deep (lateral) aspect of the tonsil is covered by the fibrous tissue of the tonsillar hemicapsule that can be easily separated throughout most of its extent from the underlying superior constrictor muscle. An important and sometimes large vein (the external palatine or paratonsillar vein) descends from the soft palate lateral to the tonsillar hemicapsule before piercing the pharyngeal wall. Haemorrhage from this vessel can complicate tonsillectomy.

The size of the tonsil varies greatly and at puberty may be approximately 10–15 mm in transverse diameter and approximately 20–25 mm in the vertical dimension. The tonsil starts to atrophy at puberty so that, by old age, only a little tonsillar lymphoid tissue remains.

A more detailed treatment of the oropharyngeal anatomy can be found in Chapter 44, Anatomy of the pharynx and oesophagus.

TONGUE

The tongue is a highly muscular organ of deglutition, taste and speech. It is partly oral and partly pharyngeal in position. It has dorsal and ventral surfaces and a root and an apex.

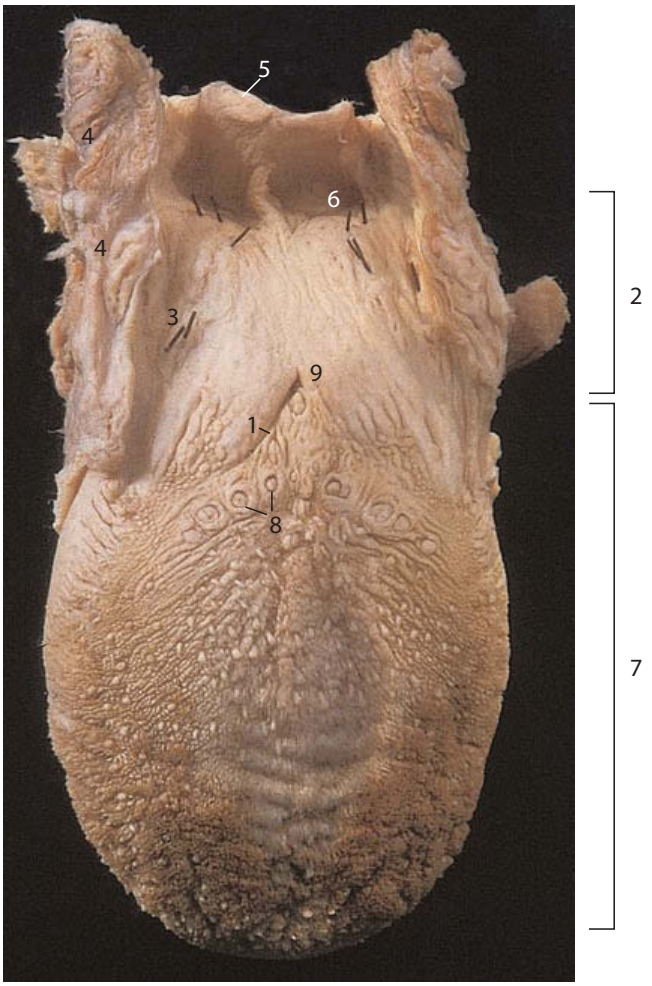

Figure 41.4 The dorsum of the tongue. 1, Sulcus terminalis; 2, posterior third (pharyngeal part); 3, lingual follicles; 4, pillars of fauces; 5, epiglottis; 6, vallecula defined by median and lateral glosso-epiglottic folds; 7, anterior two-thirds (palatine part); 8, circumvallate papillae; 9, foramen caecum. Reprinted from Ref. 2 by kind permission of Informa Healthcare.

The curved dorsum of the tongue (**Figure 41.4**) shows an anterior, oral part facing upwards and a posterior, pharyngeal part facing posteriorly, the two being separated by a V-shaped groove, the sulcus terminalis. The sulcus terminalis runs anterolaterally towards the palatoglossal arches from a median depression, the foramen caecum that indicates the site of the embryonic thyroid diverticulum that gives origin to the thyroid gland.

The anterior two-thirds of the tongue in front of the sulcus terminalis is related to the hard and soft palates above and has a tapered tip or apex touching the incisor teeth, and a margin in contact with the gums and teeth. On each side, in front of the palatoglossal arch, are four or five vertical folds, the foliate papillae. The dorsum has a longitudinal median sulcus and is papillated and the three remaining types of papillae representing the filiform, fungiform and circumvallate papillae. Of the papillae, all except the filiform papillae bear taste buds.

The keratinized filiform papillae are the most numerous. They are minute conical or cylindrical projections, arranged in diagonal rows extending anterolaterally, parallel with the sulcus terminalis, except at the apex where they are transverse. They have a masticatory function, appearing to increase the friction between the tongue and food, facilitating the movement of particles by the tongue within the oral cavity. The fungiform papillae appear scattered on the lingual margin but also irregularly on the dorsal surface, where they may occasionally be numerous. They differ from filiform papillae by their larger size, rounded (mushroom) shape and deep red colour (due to their thin, non-keratinized epithelium and highly vascular connective tissue core). The circumvallate papillae are cylindrical structures, 1–2 mm in diameter, varying in number from about 8 to 12 and form a V-shaped row immediately in front of the sulcus terminalis. Each papilla is circumscribed by a groove.

The pharyngeal (postsulcal) third of the tongue lying behind the sulcus terminalis forms the base of the tongue and lies posterior to the palatoglossal arches. It forms the anterior wall of the oropharynx and its mucosa is reflected on to the epiglottis posteriorly by a median and two lateral glossoepiglottic folds. The folds surround two depressions or valleculae. The pharyngeal part of the tongue has underlying lymphoid nodules that produce low-surface elevations collectively termed the lingual tonsil. The ducts of small seromucous glands open on the apices of these elevations.

The ventral inferior surface of the tongue (see **Figure 41.3**) is smooth, purplish and reflected on to the oral floor and gums. Anteriorly is a median mucosal fold, the lingual frenum. Lateral to this fold on either side, a deep lingual vein is visible, and lateral to the vein is a fringed mucosal ridge, the plica fimbriata.

ORAL MUCOSA

The lining of the mouth, the oral mucosa, is continuous with the skin at the vermilion of the lip and with the pharyngeal mucosa at the oropharyngeal isthmus. It varies in structure, appearance and function in different regions of the oral cavity.[1] It can be classified into masticatory, lining and specialized mucosae. Masticatory mucosa covers the gingivae (gums) and hard palate. Its epithelium is keratinized (often parakeratinized) and has a dense fibrous lamina propria. It is pink in colour. A submucosa is absent from the gingivae and the midline palatine raphe, but is present over the rest of the hard palate, especially where it contains mucous salivary glands, and also the greater palatine nerves and vessels. The masticatory mucosa is bound firmly to underlying bone or to the necks of the teeth, forming in the gingivae and palatine raphe a mucoperiosteum.

Lining mucosa covers the internal surfaces of the lips and cheeks, floor of the mouth, soft palate, ventral surface of the tongue and the alveolar processes (excluding the gingivae). It is red in colour, having a non-keratinized, stratified, squamous epithelium overlying a loosely fibrous and elastic lamina propria, and the submucosa contains some fat deposits and collections of minor mucous glands.

Gustatory mucosa covers the anterior two-thirds of the dorsum of the tongue. The vermilion (red zone) of the lip that separates the skin from lining mucosa has been regarded by some as being specialized, as it shares features of both lining and masticatory mucosa.[2] The epithelium that attaches the tooth to the gingiva, the junctional epithelium, also has features that distinguish it from all other stratified squamous epithelia (e.g. internal and external basal lamina).

MUSCLES OF THE ORAL CAVITY

Buccinator muscle

The muscle of the cheek is the buccinator (**Figure 41.5**). Above and below it is attached to the outer surfaces of the alveolar processes of the maxilla and mandible by the side of the molar teeth. Behind, it arises from the anterior margin of the pterygomandibular raphe (a thin band of tendinous fibres passing between the hamulus of the medial pterygoid plate down to the posterior end of the mylohyoid line of the mandible). Additionally, a few fibres arise from a fine tendinous band that bridges the interval between the maxilla and the pterygoid hamulus. From these origins the fibres of buccinator pass forwards towards the angle of the mouth. Here, the central fibres decussate, those from below crossing to the upper part of the mouth, those from above crossing to the lower part. The highest and lowest fibres of buccinator continue forwards to enter their corresponding lips without decussation.

The buccinator muscle compresses the cheek against the teeth and gums during mastication and assists the tongue in directing food between the teeth. When the cheeks have been distended with air, the buccinators expel it between the lips, for example, when playing wind instruments. The buccinator muscle is innervated by the buccal branch of the facial nerve. Its arterial supply is derived from the facial and maxillary (buccal branch) arteries.

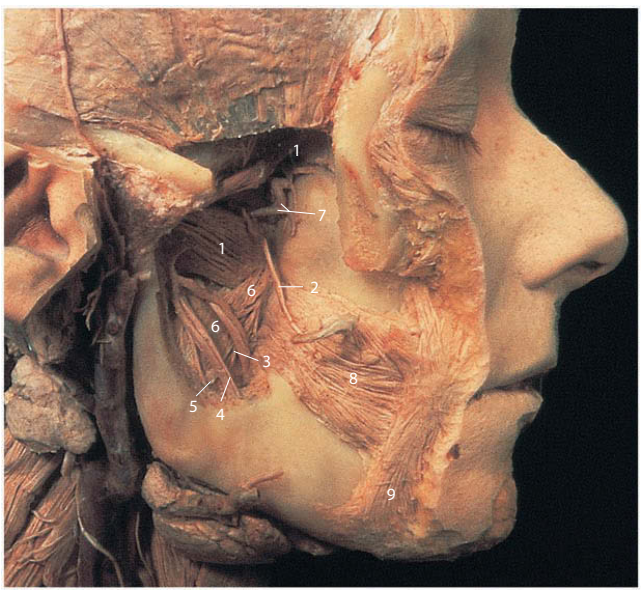

Figure 41.5 The buccinator muscle and the infratemporal fossa. 1, Lateral pterygoid muscle (two heads); 2, buccal nerve; 3, lingual nerve with accompanying branch from maxillary artery; 4, inferior alveolar nerve and artery; 5, mylohyoid nerve; 6, medial pterygoid muscle (two heads); 7, maxillary artery; 8, buccinator muscle; 9, depressor anguli oris muscle. Reprinted from Ref. 2 by kind permission of Informa Healthcare.

Mylohyoid muscle

The main muscle forming the floor of the mouth is the mylohyoid muscle (**Figures 41.6** and **41.7**). Immediately above it is the geniohyoid muscle. The mylohyoid muscle is a flat, triangular sheet attached to the mylohyoid line of the mandible. The posterior fibres pass medially and slightly downwards to the front of the body of the hyoid bone near its lower border. The middle and anterior fibres from each side decussate in a median fibrous raphe that stretches from the symphysis menti to the hyoid bone.

The mylohyoid muscle elevates the floor of the mouth in the first stage of swallowing. It also aids in elevating the hyoid bone or depressing the mandible when the hyoid bone is fixed. The muscle is supplied by the mylohyoid branch of the inferior alveolar nerve and derives its blood supply from three sources: the lingual artery (sublingual branch),

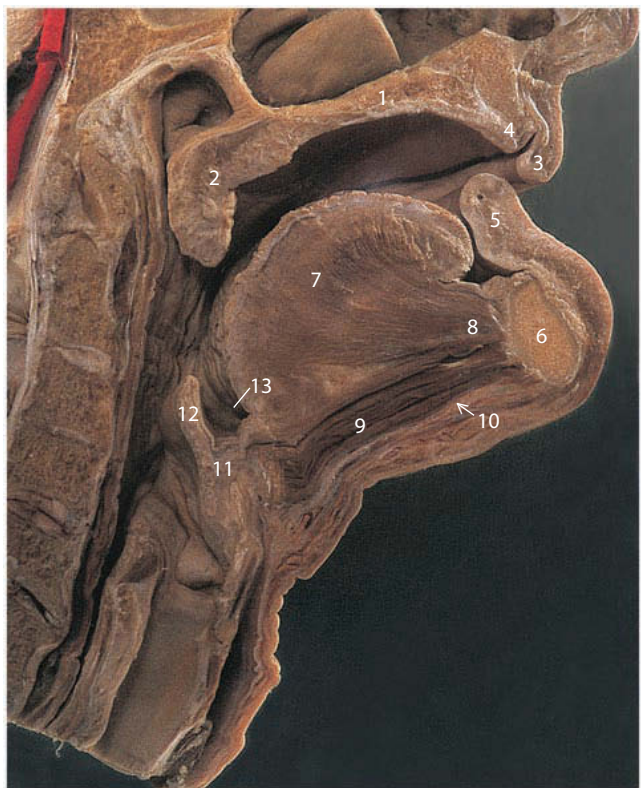

Figure 41.6 The floor of the mouth as seen in a median sagittal section through the head. 1, Hard palate; 2, soft palate; 3, upper lip and superior part of orbicularis oris muscle; 4, edentulous maxillary alveolar ridge; 5, lower lip with inferior part of orbicularis oris muscle; 6, body of mandible; 7, tongue; 8, genioglossus muscle; 9, geniohyoid muscle; 10, mylohyoid muscle; 11, hyoid bone; 12, epiglottis; 13, valeculla. Reprinted from Ref. 2 by kind permission of Informa Healthcare.

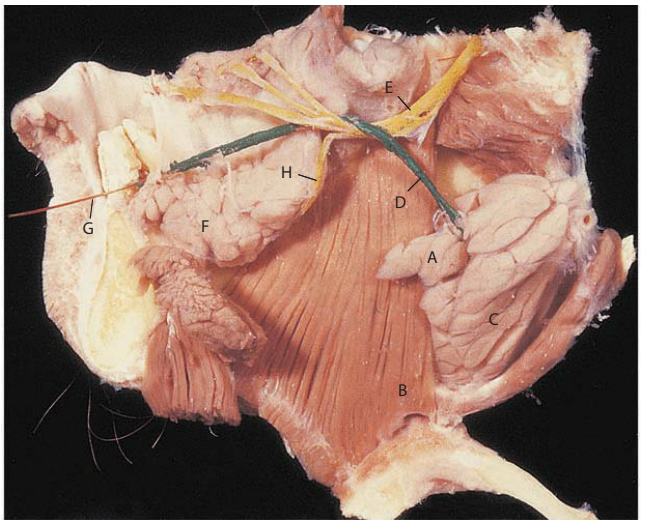

Figure 41.7 Medial view of the floor of mouth showing deep part of the submandibular gland (A) passing around the free border of the mylohyoid muscle (B). C, Superficial part of submandibular gland; D, submandibular duct wrapping around the lingual nerve (E); F, sublingual strand; G, bristle in opening of submandibular duct at the sublingual papilla; H, branches of the lingual nerve to the sublingual gland carrying parasympathetic nerve fibres. Reprinted from Ref. 1 by permission from Elsevier.

the maxillary artery (the mylohyoid branch of the inferior alveolar artery) and the facial artery (submental branch).

Geniohyoid

This narrow muscle lies above the medial part of the mylohyoid (**Figure 141.8** and see also **Figure 41.6**). It arises from the inferior genial tubercle (mental spine) on the back of the symphysis menti. It runs backwards and slightly downwards to attach to the anterior surface of the body of the hyoid bone.

The geniohyoid muscle elevates the hyoid bone and draws it forwards. When the hyoid bone is fixed, the geniohyoid muscle depresses the mandible. The muscle is supplied by the first cervical spinal nerve, through the hypoglossal nerve. The blood supply is derived from the lingual artery (sublingual branch).

Muscles of the tongue

The muscles of the tongue comprise both extrinsic and intrinsic muscles, the former extending outside the tongue and moving it bodily, the latter lying wholly within it and altering its shape.

The **extrinsic** musculature is composed of four pairs of muscles: genioglossus, hyoglossus, styloglossus and palatoglossus.

GENIOGLOSSUS MUSCLE

The genioglossus muscle lies near the midline (see **Figures 41.6** and **41.8**). It arises from the superior genial tubercle (mental spine) behind the mandibular symphysis and above the origin of the geniohyoid muscle. From its origin, the fibres fan out as they pass backwards and upwards. The inferior fibres are attached to the upper anterior surface of the hyoid body near the midline. Intermediate fibres pass backwards into the posterior part of the tongue, and superior fibres ascend forwards to enter the whole length of the ventral surface of the tongue from root to apex, intermingling with the intrinsic muscles.

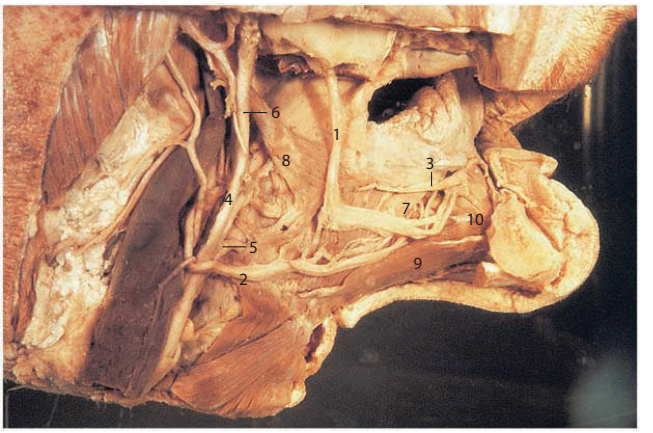

Figure 41.8 Muscles of the tongue and structures on the hyoglossus muscle in the floor of the mouth. 1, Lingual nerve; 2, hypoglossal nerve; 3, submandibular duct (cut); 4, external carotid artery; 5, lingual artery; 6, glossopharyngeal nerve (cut); 7, hyoglossus muscle; 8, styloglossus muscle; 9, geniohyoid muscle; 10, genioglossus muscle. Reprinted from Ref. 1 by permission from Elsevier.

The genioglossus muscle brings about the forward traction of the tongue to protrude its apex from the mouth. Acting bilaterally, the two muscles depress the central part of the tongue, making it concave from side to side. Acting unilaterally, the muscle helps move the tongue to the opposite side. Genioglossus receives its motor innervation from the hypoglossal nerve. Its blood supply is derived from the lingual artery (sublingual branch) and the facial artery (submental branch).

HYOGLOSSUS

This muscle arises from both the greater cornu and from the front of the body of the hyoid bone (**Figure 41.8**). It runs up to insert into the side of the tongue between the inferior longitudinal muscle medially and styloglossus laterally.

The hyoglossus muscle depresses the tongue. It is innervated by the hypoglossal nerve. Its arterial supply is derived from the lingual (sublingual branch) and the facial arteries (submental branch).

STYLOGLOSSUS

This muscle arises from near the apex of the styloid process (anterolateral aspect) and from the styloid end of the stylomandibular ligament (a fibrous cord extending from the tip of the styloid process to the lesser cornu of the hyoid bone) (**Figure 41.8**). From this origin, the muscle runs downwards and forwards to enter the substance of the tongue, decussating with fibres of hyoglossus.

The styloglossus muscle acts to pull the tongue upwards and backwards. The muscle is supplied by the hypoglossal nerve and derives its blood supply from the sublingual branch of the lingual artery.

PALATOGLOSSUS

Although this muscle is most closely associated with the soft palate in function and innervation, it is described here with the other tongue muscles. The palatoglossus arises from the palatine aponeurosis and passes to the side of the tongue within the palatoglossal arch. Acting bilaterally, the muscles narrow the oropharyngeal isthmus and can also help raise the sides of the tongue. Unlike the other tongue muscles, the palatoglossus is innervated, not by the hypoglossal nerve, but by the cranial portion of the accessory nerve through the pharyngeal plexus. Its blood supply is derived from the ascending pharyngeal and facial (ascending palatine) arteries.

INTRINSIC MUSCLES OF THE TONGUE

These comprise four groups: the superior and inferior longitudinal, the transverse and the vertical muscles.

The superior longitudinal muscle forms a thin stratum of longitudinal and oblique fibres lying beneath the lining of the dorsum of the tongue. The inferior longitudinal muscle is a narrow band of muscle beneath the inferior surface between the genioglossus and hyoglossus muscles. The transverse muscle fibres pass laterally from the median fibrous septum to the submucous fibrous tissue at the lingual margin. The vertical muscle fibres extend from the dorsal to the ventral aspects of the tongue in the borders of its anterior part.

When the superior and inferior longitudinal muscles contract, the tongue tends to shorten. In addition, the superior longitudinal fibres also pulls the apex and sides upwards to make the dorsum concave, while the inferior longitudinal fibres pull the apex down to make the dorsum convex. The transverse muscle contracts to narrow and elongate the tongue while contraction of the vertical muscle makes the tongue flatter and wider. Acting alone or in pairs and in endless combination, the intrinsic muscles give the tongue precise and highly varied mobility, important not only in alimentary function but also in speech. All intrinsic lingual muscles are supplied by the hypoglossal nerve and derive their blood supply from the lingual artery.

MUSCLES OF THE LIPS

The muscles surrounding the mouth and contributing to the lips are derived from two different sources. Neighbouring muscles of facial expression converge on the angle of the mouth and pass through into the lips. For the upper lip, these are chiefly from the buccinator and depressor anguli oris, and for the lower lip, the buccinator, levator anguli oris and zygomaticus major. In addition, an accessory muscle, incisivus labii superioris, is present in the upper lip, arising from the floor of the incisive fossa of the maxilla above the eminence of the lateral incisor tooth and running laterally within the upper lip to the modiolus (a zone of muscle intersection just beyond the corner of the mouth). A similar strip of muscle is present in the lower lip, incisivus labii inferioris, arising from the floor of the incisive fossa of the mandible and running laterally within the lip to the modiolus.

The muscles of the mouth are capable of various movements, including closing, protrusion and pursing of the lips. The muscles are innervated by the facial nerve (buccal and mandibular branches) and derive their blood supply from the facial (superior and inferior labial), maxillary (mental and infraorbital branches) and superficial temporal arteries.

VASCULAR SUPPLY AND LYMPHATIC DRAINAGE OF THE ORAL CAVITY

Arteries

The main arteries to the teeth, palate and cheeks are derived chiefly from the maxillary artery, a terminal branch of the external carotid. The lips are mainly supplied by the superior and inferior labial branches of the facial artery. The floor of the mouth and tongue are supplied by the lingual arteries. The cheek is supplied by the buccal branch of the maxillary artery.

Teeth in the lower jaw are supplied by the inferior alveolar (dental) artery, a branch of the maxillary artery (see **Figure 41.5**). It lies in the infratemporal fossa where it gives off a mylohyoid branch before entering the mandibular foramen. The inferior alveolar artery then traverses the mandibular canal (accompanied by the inferior alveolar nerve) to supply the mandibular molars and premolars and divides into the incisive and mental branches below the premolar teeth. The incisive branch continues below the incisor teeth (which it supplies) to the midline. The mental artery leaves the mental foramen to supply the chin.

Teeth in the upper jaw are supplied by the posterior, middle and anterior superior alveolar (dental) arteries that form a plexus of vessels. The posterior superior alveolar artery usually arises from the third part of the maxillary artery in the pterygopalatine fossa. It descends on the infratemporal surface of the maxilla to supply molar and premolar teeth, adjacent bone and the maxillary sinus, and provides superficial branches that continue over the alveolar process to supply the gingivae. The anterior superior alveolar artery arises from the infraorbital artery that enters the orbit posteriorly through the inferior orbital fissure to run in the infraorbital groove and canal with the infraorbital nerve. It curves through a fine canal (canalis sinuosus) to supply the upper incisor and canine teeth and the mucous membrane in the maxillary sinus. A middle superior alveolar artery is often present and supplies the premolar teeth.

The gingival tissues derive their blood supply from the maxillary and lingual arteries. In the lower jaw, the buccal gingiva posteriorly is supplied by the buccal artery (a branch of the maxillary artery as it crosses the lateral pterygoid muscle) and by perforating branches from the

inferior alveolar artery. Anteriorly, the labial gingiva is supplied by the mental artery and by perforating branches of the incisive artery. The lingual gingiva is supplied by perforating branches from the inferior alveolar artery and by the lingual artery of the external carotid.

In the upper jaw, the buccal gingiva around the molar and premolar teeth are supplied by gingival and perforating branches from the posterior and middle superior alveolar arteries and by the buccal artery. The labial gingiva of the anterior teeth is supplied by labial branches of the infraorbital artery and by perforating branches of the anterior superior alveolar artery. The palatal gingiva around the maxillary teeth is supplied primarily by branches of the greater palatine artery, a branch of the third part of the maxillary artery in the pterygopalatine fossa.

The hard palate derives its blood supply principally from the greater palatine artery, a branch of the third part of the maxillary artery. The greater palatine artery descends (with its accompanying nerve) in the palatine canal. In the canal, it gives off two or three lesser palatine arteries that are transmitted through lesser palatine canals to supply the soft palate and tonsil (anastomosing with the ascending palatine branch of the facial artery). The greater palatine artery emerges on to the oral surface of the palate at the greater palatine foramen and runs in a curved groove near the alveolar border of the hard palate to the incisive canal. It ascends this canal and anastomoses with septal branches of the nasopalatine artery.

The tongue and floor of mouth are supplied mainly by the lingual artery that arises in the neck from the external carotid artery (see **Figure 41.8**). It reaches the floor of the mouth by passing between the hyoglossus muscle and the middle constrictor of the pharynx. Near the tip of the tongue, the lingual artery anastomoses with its fellow from the opposite side. The branches of the lingual artery in the floor of the mouth are the dorsal lingual branches, the sublingual artery and the deep lingual artery.

The dorsal lingual arteries (usually two or three) arise medial to the hyoglossus muscle and ascend to the posterior part of the dorsum of the tongue. They supply the mucous membrane of the dorsum of the tongue, the palatoglossal arch, soft palate, tonsil and epiglottis.

The sublingual artery arises from the lingual artery at the anterior margin of hyoglossus. It passes forwards between the genioglossus and mylohyoid muscles to the sublingual gland. It also provides a branch that enters a small foramen (lingual foramen) on the mandible, situated in the midline on the posterior aspect of the symphysis, immediately above the genial tubercles.

The deep lingual artery is the terminal part of the lingual artery and is found on the inferior surface of the tongue near the lingual frenum.

In addition to the lingual artery, the tonsillar and ascending palatine branches of the facial and ascending pharyngeal arteries also supply tissue in the root of the tongue. In the region of the valleculae, epiglottic branches of the superior laryngeal artery anastomose with the inferior dorsal branches of the lingual artery.

Veins

As with veins elsewhere in the body, the pattern of drainage for the mouth and associated structures is variable and only a generalized account will be given.

The cheek is drained by the buccal vein that leads to the pterygoid venous plexus in the infratemporal fossa. Venous blood from the lips is collected by the superior and inferior labial veins and drains into the facial vein. The veins of the hard palate accompany the arteries and drain largely to the pterygoid plexus.

Veins accompanying the superior alveolar arteries drain the upper jaw and teeth anteriorly into the facial vein, or posteriorly into the pterygoid venous plexus.

Veins from the lower jaw and teeth collect into several inferior alveolar veins. Some of these veins drain through the mental foramen to the facial vein, others via the mandibular foramen to the pterygoid venous plexus.

No accurate description is available concerning the venous drainage of the gingivae, although it may be assumed that buccal, lingual, greater palatine and nasopalatine veins are involved. These veins run into the pterygoid plexuses (apart from the lingual veins, which pass directly into the internal jugular veins).

There are two sets of veins draining the tongue. The deep lingual vein begins near the apex of the tongue and runs back on its ventral surface (see **Figure 41.3**). It joins a sublingual vein from the sublingual salivary gland, to form the vena comitans nervi hypoglossi. This then passes backwards with the hypoglossal nerve and joins the lingual, facial or internal jugular vein. Dorsal lingual veins drain the dorsum and sides of the tongue and join the lingual veins accompanying the lingual artery. They drain into the internal jugular in the region of the hyoid bone.

Lymph drainage

The principal sites of drainage of lymphatic vessels from orodental tissues are the submental, submandibular and jugulodigastric lymph nodes. However, the manner of drainage is so variable that there is no precise and accurate description.

The cheek, upper lip and lateral parts of the lower lip drain to the submandibular nodes. The central part of the lower lip drains to the submental nodes.

The lymph vessels from the teeth usually run directly into the submandibular lymph nodes on the same side. Lymph from the mandibular incisors, however, drains into the submental lymph nodes. Occasionally, lymph from the molars may pass directly into the jugulodigastric group of nodes.

The lingual and palatal gingivae drain into the jugulodigastric group of nodes, either directly or indirectly through the submandibular nodes. Lymphatics from the bulk of the palate terminate in the jugulodigastric group of nodes.

The lymphatics from the tongue drain to three main regions: marginal, central and dorsal. The anterior region of the tongue drains into the marginal and central vessels

and, behind the circumvallate papillae, the posterior part of the tongue drains into the dorsal lymph vessels. Of particular clinical importance is appreciating that more central regions may drain both ipsilaterally and contralaterally.

Marginal lymph vessels of the tongue that arise from the apex of the tongue and the **lingual frenum area descend under the mucosa to widely distributed nodes.**

- Some vessels enter the submental nodes and also pass to the jugulo-omohyoid nodes. Vessels may cross under the frenulum to end in the contralateral nodes, efferent vessels of submental nodes that are median pass to both sides.
- Some vessels drain to submandibular nodes.
- Some vessels end in jugulodigastric nodes, one vessel often reaching the jugulo-omohyoid node.

Vessels from the lateral margin of the tongue may drain into the submandibular nodes while others end in the jugulodigastric or jugulo-omohyoid nodes. Vessels from the posterior part of the lingual margin traverse the pharyngeal wall to the jugulodigastric lymph nodes.

Vessels draining the central region of the tongue may drain to either or both sides into the deep cervical nodes, especially the jugulodigastric and jugulo-omohyoid nodes. Some pierce the mylohyoid muscle to enter the submandibular nodes.

Vessels draining the dorsum of the tongue in the region of the circumvallate papillae and behind them run posteroinferiorly. Those near the median plane may pass to either or both sides, draining to the jugulodigastric and jugulo-omohyoid lymph nodes.

Innervation

The mucosa lining the mouth derives its sensory innervation chiefly from the maxillary and mandibular divisions of the trigeminal nerve. Additional nerves supply the tongue, including special taste sensation. The muscles of the mouth are supplied chiefly by the mandibular, facial and hypoglossal nerves. The salivary glands are supplied by secretomotor fibres derived from the facial and glossopharyngeal nerves. The innervation of the oral musculature is shown in **Table 41.1**.

SENSORY SUPPLY

Cheeks, lips and palate

The sensory supply to the cheek is derived from the buccal branch of the mandibular nerve (see **Figure 41.5**). This nerve arises from the anterior division of the mandibular nerve within the infratemporal fossa. Initially deep to the lateral pterygoid muscle, it emerges between the two heads of the muscle and runs forwards to supply the mucosa of the cheeks.

The upper lip is supplied by the infraorbital branch of the maxillary nerve (**Figure 41.9**). Running along the floor of the orbit in the infraorbital canal, it enters the face at the infraorbital foramen, where its labial branch runs downwards to supply the upper lip. The mental nerve is a terminal branch of the inferior alveolar nerve and exits the mandible at the mental foramen to supply the lower lip (see **Figure 41.9**).

The sensory nerves to the palate are derived from the greater and lesser palatine and nasopalatine branches of the maxillary nerve (**Figure 41.10**) These nerves pass through the pterygopalatine ganglion. The greater palatine nerve descends through the greater palatine canal, entering the hard palate at the greater palatine foramen. It then passes forwards on the bony palate towards the canine tooth, supplying the gums and the mucosa and

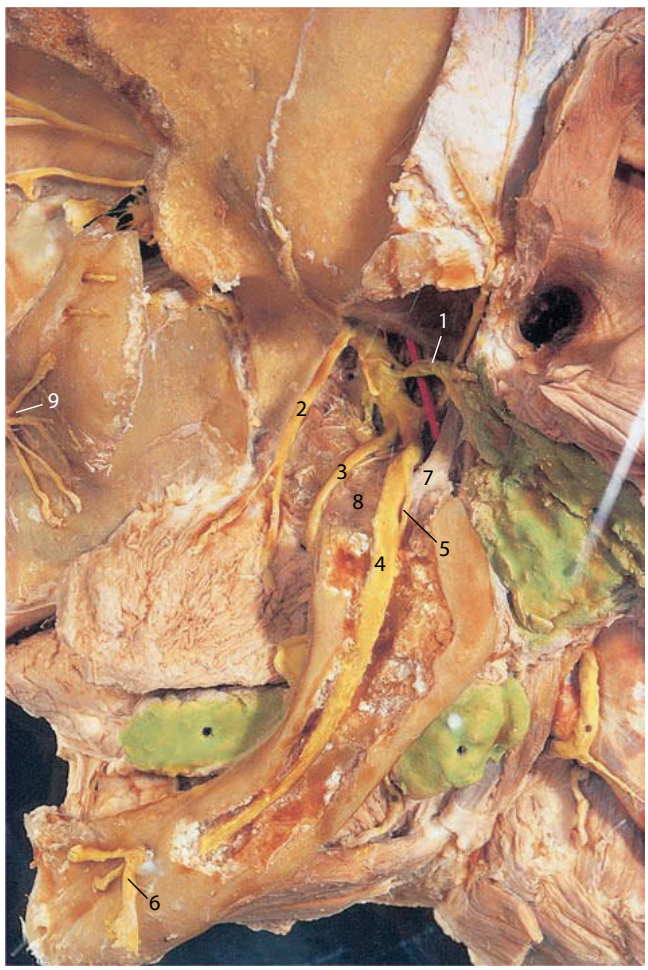

Figure 41.9 Infratemporal fossa showing mandibular nerve branches. 1, Auriculotemporal nerve surrounding middle meningeal artery; 2, buccal nerve; 3, lingual nerve (joined by chorda tympani nerve); 4, inferior alveolar nerve; 5, mylohyoid nerve; 6, mental nerve; 7, sphenomandibular ligament; 8, medial pterygoid muscle; 9, infraorbital nerve. Reprinted from Ref. 1 by permission from Elsevier.

TABLE 41.1 Innervation of the oral musculature

Region	Muscle	Nerve
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glands of the hard palate (excluding the anterior teeth). As it leaves the greater palatine canal, palatine branches are also distributed to the soft palate. The smaller lesser palatine nerves descend through the greater palatine canal to emerge through the inconspicuous lesser palatine foramina and give branches to the uvula, tonsil and soft palate. Fibres conveying taste impulses from the palate probably pass via the palatine nerves to the pterygopalatine ganglion (see **Figure 41.10**) and through it to the nerve of the pterygoid canal and then the greater petrosal nerve to reach the facial ganglion, where their somata are situated. Parasympathetic postganglionic secretomotor fibres run in the facial nerve through its greater petrosal nerve to reach the pterygopalatine ganglion to be distributed in the palatine nerves, thereby reaching palatine mucous glands.

The nasopalatine nerves (**Figure 41.10**) enter the palate at the incisive foramen to supply the anterior part of the hard palate behind the incisor teeth.

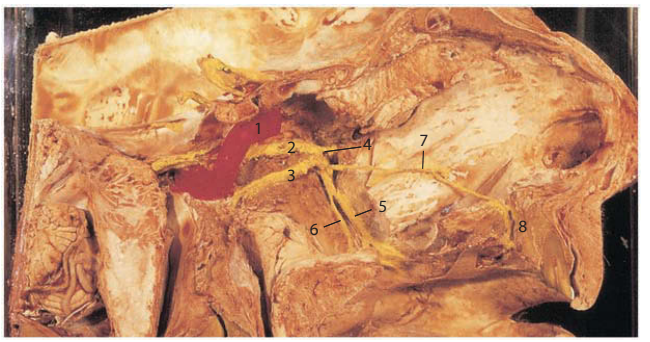

Figure 41.10 The pterygopalatine ganglion. 1, Internal carotid artery; 2, maxillary nerve; 3, nerve of pterygoid canal; 4, pterygopalatine ganglion; 5, greater palatine nerve; 6, lesser palatine nerve; 7, nasopalatine nerve dissected off from nasal septum; 8, nasopalatine nerve at incisive fossa. Reprinted from Ref. 1 by permission from Elsevier.

There is an additional sensory component in the region of the pillars of the fauces derived from the glossopharyngeal nerve which is involved in the gag reflex (see **Figure 41.8**).

The floor of the mouth is supplied by the lingual nerve (see **Figures 41.5** and **41.9**). This nerve arises from the posterior division of the mandibular nerve in the infratemporal fossa.

Teeth and gingivae

The regional supply to the teeth and gingivae is shown in **Table 41.2**. The posterior superior alveolar nerves supply the teeth in the upper jaw, while the inferior alveolar nerve supplies those in the lower jaw.

There are three superior alveolar (dental) nerves that arise from the maxillary nerve in the pterygopalatine fossa or in the infraorbital groove (canal) and these form a plexus of nerves supplying all the upper teeth. The posterior superior alveolar (dental) nerve leaves the maxillary nerve in the pterygopalatine fossa and runs anteroinferiorly to pierce the infratemporal surface of the maxilla, descending under the mucosa of the maxillary sinus. After supplying the lining of the sinus, the nerve divides into small branches that link up as the molar part of the superior dental plexus, supplying twigs to the molar teeth. It also supplies a branch to the upper gingiva and the adjoining part of the cheek.

The variable middle superior alveolar (dental) nerve arises from the infraorbital nerve as it runs in the infraorbital groove, and passes downwards and forwards in the lateral wall of the maxillary sinus. It ends in small branches that unite with the superior dental plexus, supplying small rami to the upper premolar teeth.

The anterior superior alveolar (dental) nerve leaves the lateral side of the infraorbital nerve near the midpoint of its canal and traverses the canalis sinuosus in the anterior wall of the maxillary sinus. Curving first under the infraorbital foramen, it passes medially towards the nose,

TABLE 41.2 Nerve supply to the teeth and gingiva

	Nasopalatine nerve			**Greater palatine nerve**					**Palatal gingival**
Maxilla	Anterior superior alveolar nerve			Middle superior alveolar nerve		Posterior superior alveolar nerve			Teeth
	Infraorbital nerve			Posterior superior alveolar nerve and buccal nerve					Buccal gingival
	1	2	3	4	5	6	7	8	Tooth position
	Mental nerve			Buccal nerve and perforating branches of inferior alveolar nerve					Buccal gingival
Mandible	Incisive nerve		Inferior alveolar nerve						Teeth
	Lingual nerve and perforating branches of inferior alveolar nerve								Lingual gingiva

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turns downwards and divides into branches supplying the incisor and canine teeth. It assists in the formation of the superior dental plexus.

The inferior alveolar (dental) nerve arises from the posterior division of the mandibular nerve in the infratemporal fossa (see **Figures 41.5** and **41.9**). Emerging from beneath the lower head of the lateral pterygoid muscle, it descends to enter the mandibular canal via the mandibular foramen (accompanied by the inferior alveolar artery). Just before entering the mandibular canal, the inferior alveolar nerve gives off a small mylohyoid branch to supply the mylohyoid muscle and the anterior belly of digastric.

In the mandibular canal, the inferior alveolar nerve runs downwards and forwards, generally below the apices of the cheek teeth until, below premolar teeth, it divides into terminal incisive and mental branches. The incisive branch continues forwards in a bony canal or in a plexiform arrangement, giving off branches to the first premolar, canine and incisor teeth, and the associated labial gingivae. The lower central incisor teeth may receive a bilateral innervation, fibres probably crossing the midline within the periosteum to re-enter the bone via numerous canals in the labial cortical plate.

The mental nerve passes upwards, backwards and outwards to emerge from the mandible via the mental foramen between and just below the apices of the premolar teeth to supply the skin of the lower lip and chin (see **Figure 41.9**).

The nerves supplying the gingiva in the upper jaw come from the maxillary nerve via its greater palatine, nasopalatine and anterior, middle and posterior superior alveolar branches. The mandibular nerve innervates the gingiva in the lower jaw by its inferior alveolar, lingual and buccal branches (see **Table 41.2**).

The tongue and floor of the mouth

The sensory supply to the tongue involves both general and taste afferents and reflects the embryological development of the structure. Thus, it can be considered in two portions, the presulcal (anterior two-thirds) and a postsulcal (posterior one-third). The nerve of general sensation to the presulcal part is the lingual nerve, indicating the embryological derivation of this part from the first branchial arch. The lingual nerve also carries taste sensation derived from the chorda tympani branch of the facial nerve. The main nerve supplying general (and taste) sensation to the postsulcal part is the glossopharyngeal nerve, while an additional area in the region of the valleculae is supplied by the internal laryngeal branch of the vagus nerve, indicating the embryological derivation of the postsulcal part from the third and fourth branchial arches.

The lingual nerve originates from the posterior trunk of the mandibular nerve in the infratemporal fossa (see **Figures 41.5**, **41.8** and **41.9**). Here, it is joined by the chorda tympani branch of the facial nerve that supplies taste to the anterior two-thirds of the tongue and parasympathetic fibres that supply the submandibular and sublingual glands via the submandibular ganglion (**Figure 41.9**). Emerging from beneath the lower head of the lateral pterygoid muscle (**Figure 41.5**), the lingual nerve passes forwards medial to the inferior alveolar nerve and is closely applied to the periosteum of the medial surface of the mandible by the side of the roots of the third molar tooth (**Figure 41.7**). Here, the lingual nerve is at great risk during surgical removal of (impacted) lower third molars using a lingual approach. The lingual nerve then passes medial to the mandibular origin of the mylohyoid muscle, which carries it progressively away from the mandible. It passes downwards and forwards on the deep surface of the mylohyoid muscle and then runs below the submandibular duct, which crosses it from medial to lateral (**Figure 41.7**). The nerve next curves upwards, forwards and medially to enter the tongue. The lingual nerve is connected to the submandibular ganglion by two or three branches and, at the anterior margin of the hyoglossus, it forms connecting loops with twigs of the hypoglossal nerve.

Branches of the lingual nerve supply the lingual gingivae, the mucosa of the floor of the mouth and the anterior two-thirds (presulcal part) of the tongue (excluding the circumvallate papillae, which are supplied by the glossopharyngeal nerve).

The glossopharyngeal nerve is present in the neck where it passes around the posterior border of the stylopharyngeus muscle, which it supplies (**Figure 41.8**). It runs forwards on this muscle and either pierces the lower fibres of the superior constrictor muscle or passes between it and the middle constrictor to be distributed to the postsulcal part of the tongue (including the circumvallate papillae). It communicates with the lingual nerve.

The sensory supply to the valleculae of the tongue (the recess between the median and lateral glossoepiglottic folds) is derived from the internal laryngeal nerve. This nerve is a branch of the superior laryngeal nerve and, passing between the superior and inferior constrictor muscles, pierces the thyrohyoid membrane. From here, branches ascend to supply the valleculae.

The parasympathetic innervation of the lingual glands is derived from the chorda tympani branch of the facial nerve that joins the lingual nerve (**Figure 41.9**) and synapses in the submandibular ganglion. Postganglionic fibres re-enter the lingual nerve to the glands. The sympathetic supply to lingual glands and vessels enters the tongue through plexuses around its arteries, arising from the carotid plexus.

MOTOR SUPPLY

The nerves supplying the buccinator and orbicularis oris muscles are derived from the facial nerve that exits the skull at the stylomastoid foramen and then passes into the substance of the parotid gland, where it divides into its terminal branches. The buccinator is supplied by its buccal branch(es) and the lips from the buccal and mandibular branches. The nerve supplying the mylohyoid muscle is the mylohyoid nerve and is seen branching from the inferior alveolar nerve just above the mandibular foramen (**Table 41.1**).

The muscles of the tongue are supplied by the hypoglossal nerve. These muscles develop primarily from occipital

somites that migrate into the developing tongue carrying their nerve supply, the hypoglossal nerve, with them. The hypoglossal nerve is seen in the neck crossing over the internal and external carotid and then the loop of the lingual artery (**Figure 41.8**). It then passes upwards and forwards between the mylohyoid and hyoglossus muscles. Here, the hypoglossal nerve is situated below the deep part of the submandibular gland, the submandibular duct and the lingual nerve. It then passes on to the lateral aspect of the genioglossus muscle, continuing forwards in its substance as far as the tip of the tongue.

The muscular branches from the hypoglossal nerve are distributed to styloglossus, hyoglossus and genioglossus. Numerous slender rami ascend into the tongue to supply its intrinsic muscles.

The nerve to geniohyoid (and to thyrohyoid) arises near the posterior border of the hyoglossus. It is derived from fibres of the first cervical spinal nerve.

TEETH

There are two generations of teeth: the deciduous (primary) dentition and the permanent (secondary) dentition. In the complete deciduous dentition there are 20 teeth – five in each jaw quadrant. In the complete permanent dentition there are 32 teeth – eight in each jaw quadrant. In both dentitions, there are three basic tooth forms: incisiform, caniniform and molariform. Incisiform teeth (incisors) are cutting teeth, having thin, blade-like crowns. Caniniform teeth (canines) are piercing or tearing teeth, having a single, stout, pointed, cone-shaped crown. Molariform teeth (molars and premolars) are grinding teeth possessing a number of cusps separated by fissures. Premolars are bicuspid teeth that are peculiar to the permanent dentition and replace the deciduous molars.

Permanent teeth

There are two incisors, a central and a lateral, in each half jaw or quadrant (**Figures 41.11** and **41.12**). Viewed from the front, the crowns are trapezoid, the maxillary incisors (particularly the central) being larger than the mandibular. They are surmounted by the biting or incisal edges. In side view their labial profiles are convex while their lingual surfaces are concavo-convex (the convexity near the cervical margin being due to a low ridge or cingulum, prominent only on upper incisors). The roots of incisors are single and rounded in maxillary teeth, but flattened mesiodistally in mandibular teeth. The upper lateral incisor may be congenitally absent or may have a reduced form (peg-shaped lateral incisor).

Behind each lateral incisor is a canine tooth with a single cusp (hence the American term cuspid) instead of an incisal edge. The maxillary canine is stouter and more pointed than the mandibular canine. The canine root is single and is the longest of any tooth.

Behind the canines are two premolars, each with a buccal and lingual cusp (hence the term bicuspid). The occlusal surfaces of the maxillary premolars are oval (the long axis is buccopalatal) with a mesiodistal fissure separating the two cusps. The maxillary first premolar usually has two roots (one buccal, one palatal). The maxillary second premolar usually has one root. The occlusal surfaces of the mandibular premolars are more circular or squarer than those of the uppers. The buccal cusp of the mandibular first premolar towers above the very much reduced lingual cusp. In the mandibular second premolar, the lingual cusp is more substantial compared with the first, and frequently presents as two cusps. Each lower premolar tooth generally has one root.

Posterior to the premolars are three molars whose size decreases as one passes backwards. Each has a large

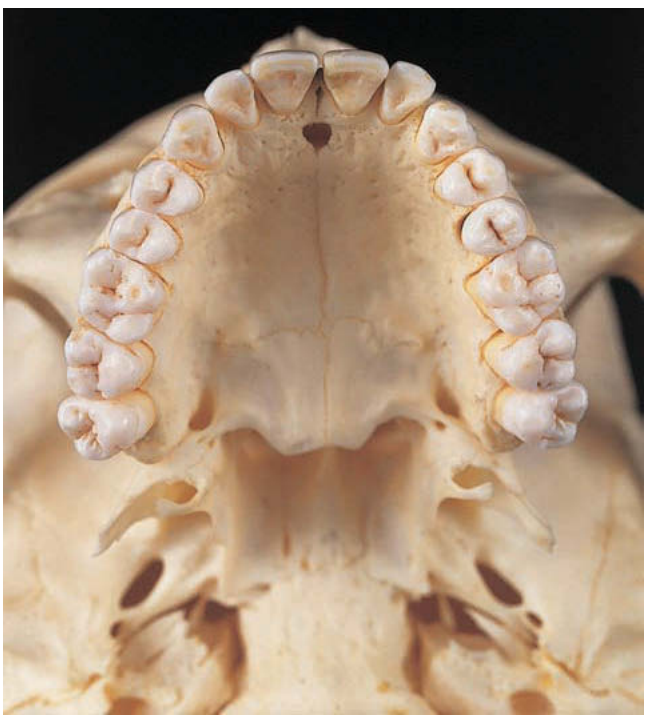


Figure 41.11 Permanent dentition upper jaw. Reprinted from Ref. 1 by permission from Elsevier.

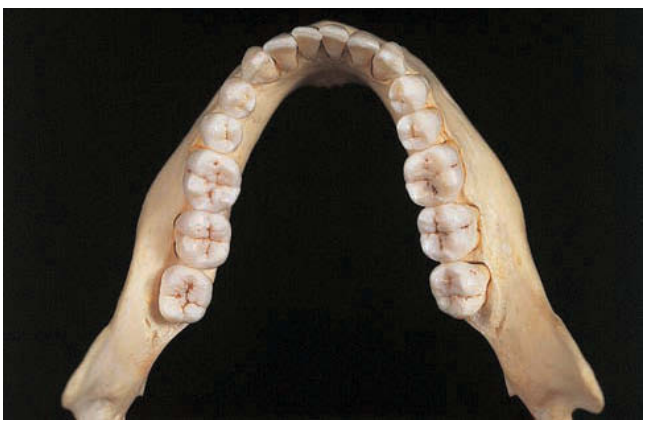


Figure 41.12 Permanent dentition lower jaw. Reprinted from Ref. 1 by permission from Elsevier.

rhomboid (upper jaw) or rectangular (lower jaw) occlusal surface with four or five cusps. The maxillary first molar has a cusp at each corner of its occlusal surface and the mesiopalatal cusp is connected to the distobuccal by an oblique ridge. A smaller cusplet or tubercle (cusplet of Carabelli) usually appears on the mesiopalatal cusp. The tooth has three widely separated roots, two buccal and one palatal. The smaller maxillary second molar has a reduced distopalatal cusp. Its three roots are less divergent and two of them may be fused. The maxillary third molar, the smallest, is very variable in form. It usually has three cusps (the distopalatal being absent) and commonly the three roots are fused.

The mandibular first molar has three buccal and two lingual cusps on its rectangular occlusal surface, the smallest cusp being distal. It has two widely separated roots, one mesial and one distal. The smaller mandibular second molar is like the first but has only four cusps (lacking the distal cusp of the first molar) and its two roots are closer together. The mandibular third molar is smaller still and, like the upper third molar, is variable in form. Its crown may resemble that of the lower first or second molar and its roots are frequently fused. The third molar is often impacted against the second molar, with resultant food packing and inflammation. Third molars are frequently congenitally absent.

Deciduous teeth

The incisors, canine and premolars of the permanent dentition replace two deciduous incisors, a deciduous canine and two deciduous molars in each jaw quadrant. The deciduous incisors and canine are shaped like their successors but are smaller and whiter and become extremely worn in older children. The deciduous second molars resemble permanent ones rather than their successors, the premolars. Each second deciduous molar has a crown almost identical to that of their respective, adjacent first permanent molar. The upper first deciduous molar has a triangular occlusal surface (its rounded 'apex' being palatal) and a fissure separates a double buccal cusp from the palatal cusp. The lower first deciduous molar is long and narrow; its two buccal cusps are separated from the two lingual cusps by a zigzagging mesiodistal fissure. Like permanent molars, upper deciduous molars have three roots and lower deciduous molars have two roots. These roots diverge more than those of permanent teeth, as each developing premolar tooth crown is accommodated directly under the crown of its deciduous predecessor. The roots of deciduous teeth are progressively resorbed by osteoclast-like cells (odontoclasts) prior to being shed.

Eruption

The first deciduous teeth to erupt into the mouth appear at approximately 6 months after birth and, by around the age of 3 years, all the deciduous teeth have erupted. By 6 years of age, the first permanent teeth appear (lower incisors and first molars) and thence the deciduous teeth are exfoliated one by one as they are replaced by their permanent successors. A complete permanent dentition is present when the third molars erupt at around the age of 18–21 years. Information on the sequence of development and eruption of teeth into the oral cavity may be important in forensic medicine and archaeology in helping to age individuals. The data provided in **Tables 41.3** and **41.4** concerning the chronology of tooth development are largely based on European-derived populations and there is evidence of ethnic variation. When a permanent tooth erupts, approximately two-thirds of the root is formed and it takes approximately another 3 years for the root to be completed. For deciduous teeth, root completion is more rapid. The developmental stages of initial calcification and crown completion are less affected by environmental influences than eruption, the timing of which may be modified by several factors such as early tooth loss and severe malnutrition.

Figures 41.13 and **41.14** show the panoramic appearance of the dentition seen with orthopantomograms at 5 and 11 years of age.

For detailed information concerning the structure and function of teeth the reader is referred to standard textbooks.[1]

TABLE 41.3 Chronology of the deciduous dentitions

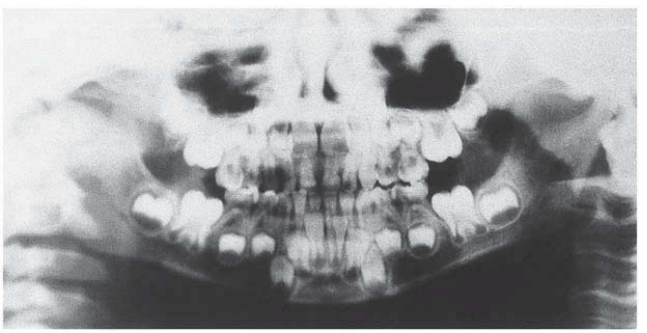
Tooth	First evidence of calcification (months IU)	Crown completed (months)	Eruption (months)	Root completed (years)
Maxillary				
A	3–4	4	7	$1\frac{1}{2}$–2
B	$4\frac{1}{2}$	5	8	$1\frac{1}{2}$–2
C	5	9	16–20	$2\frac{1}{2}$–3
D	5	6	12–16	2–$2\frac{1}{2}$
E	6–7	10–12	21–30	3
Mandibular				
A	$4\frac{1}{2}$	4	$6\frac{1}{2}$	$1\frac{1}{2}$–2
B	$4\frac{1}{2}$	$4\frac{1}{2}$	7	$1\frac{1}{2}$–2
C	5	9	16–20	$2\frac{1}{2}$–3
D	5	6	12–16	2–$2\frac{1}{2}$
E	6	10–12	21–30	3

Unless otherwise indicated all dates are post-partum. IU, *in utero*. The teeth are identified according to the Zsigmondy System. Reprinted from Ref. 1 by permission from Elsevier.

TABLE 41.4 Chronology of the permanent dentitions

Tooth	First evidence of calcification	Crown completed (years)	Eruption (years)	Root completed (years)
Maxillary				
1	3–4 months	4–5	7–8	10
2	10–12 months	4–5	8–9	11
3	4–5 months	6–7	11–12	13–15
4	$1\frac{1}{2}-1\frac{3}{4}$ years	5–6	10–11	12–13
5	$2-2\frac{1}{2}$ years	6–7	10–12	12–14
6	Birth	$2\frac{1}{2}$ –3	6–7	9–10
7	$2\frac{1}{2}$ –3 years	7–8	12–13	14–16
8	7–9 years	12–16	17–21	18–25
Mandibular				
1	3–4 months	4–5	6–7	9
2	3–4 months	4–5	7–8	10
3	4–5 months	6–7	9–10	12–14
4	$1\frac{3}{4}$ –2 years	5–6	10–12	12–13
5	$2\frac{1}{4}-2\frac{1}{2}$ years	6–7	11–12	13–14
6	Birth	$2\frac{1}{2}$ –3	6–7	9–10
7	$2\frac{1}{2}$ –3 years	7–8	12–13	14–15
8	8–10 years	12–16	17–21	18–25

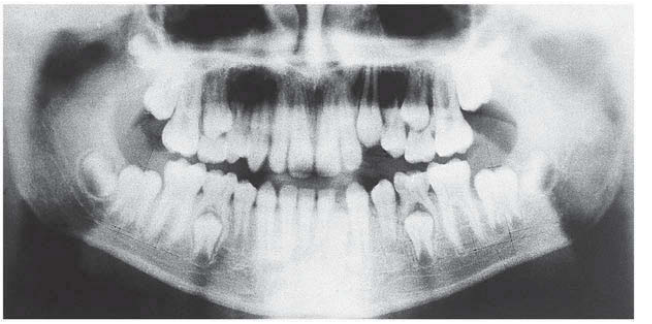
All dates are post-partum. The teeth are identified according to the Zsigmondy System. Reprinted from Ref. 1 by permission from Elsevier.



Teeth erupted Max ABCDE / Mand. ABCDE

Teeth unerupted Max 1234567 / Mand. 1234567

Figure 41.13 Orthopantomogram from patient aged 5 years. Reprinted from Ref. 1 by permission from Elsevier.



Teeth erupted Max 1234E6 / Mand. 1234E6

Teeth unerupted Max 578 / Mand. 578

Figure 41.14 Orthopantomogram from patient aged 11 years. Reprinted from Ref. 1 by permission from Elsevier.

TISSUE SPACES AROUND THE JAWS

The most common cause of infection of the tissues associated with the mouth is dental caries (tooth decay). As infection may spread from the teeth to the head and neck and become life-threatening, a knowledge of the tissue spaces associated with the jaws is of considerable clinical importance.[3–6] The tissue 'spaces' are only potential spaces that are normally occupied by loose connective tissue. It is only when inflammatory products destroy the loose connective tissue that a definable space is produced. The tissue spaces associated with the mouth are primarily defined by muscles (principally the mylohyoid, buccinator, masseter, medial pterygoid, superior constrictor and orbicularis oris muscles). Knowledge of the normal position of the root apices in relation to some of these muscles is important for an appreciation of the treatment of dental abscesses.[7]

Because of the potential of inflammation associated with the tissues surrounding partially erupted, impacted third molars (pericoronitis), the spaces associated with this region are particularly important and, as they are interconnected, inflammation can spread to involve the tissue spaces of the neck. The submental and submandibular tissue spaces are located below the inferior border of the mandible, beneath the mylohyoid muscle, in the suprahyoid region of the neck. The submental space lies beneath the chin in the midline, between the mylohyoid muscles and the investing layer of deep cervical fascia. It is bounded laterally by the two anterior bellies of the digastric muscles. The submental space communicates posteriorly with the two submandibular spaces. The submandibular space is situated between the anterior and posterior bellies of the digastric muscle. It communicates with the sublingual space around the posterior free border of the mylohyoid muscle.

The sublingual space lies in the floor of the mouth, above the mylohyoid muscles. It is continuous across the midline and communicates with the submandibular spaces over the posterior free borders of the mylohyoid muscles (see **Figure 41.7**).

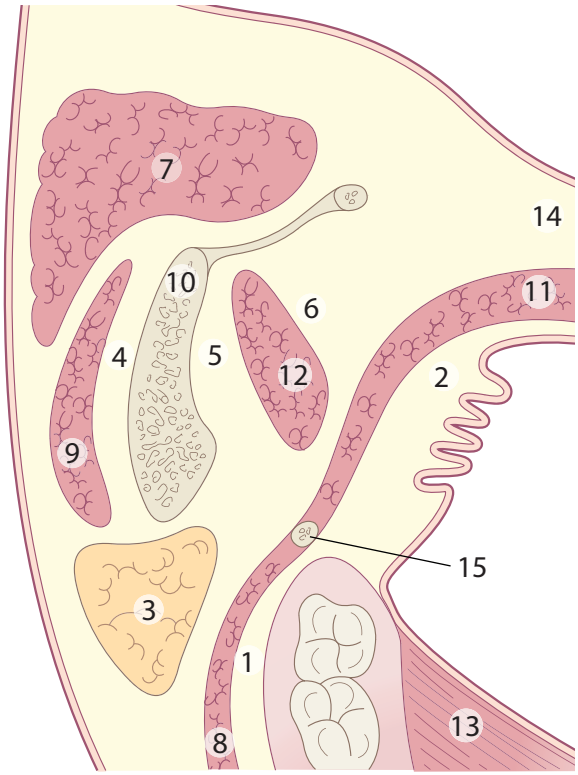


Figure 41.15 Diagram showing the tissue spaces in the retromandibular region. 1, Vestibular sulcus; 2, peritonsillar space; 3, buccal space, filled with buccal pad of fat; 4, submasseteric spaces; 5, pterygomandibular space; 6, parapharyngeal space; 7, parotid space; 8, buccinator muscle; 9, masseter muscle; 10, ramus of mandible; 11, superior constrictor of pharynx; 12, medial pterygoid muscle; 13, mylohyoid muscle; 14, retropharyngeal space; 15, pterygomandibular raphe.

The remaining tissue spaces in the region of the molar teeth are illustrated in **Figure 41.15**. The buccal space is located in the cheek, on the lateral side of the buccinator muscle.

Between the lateral surface of the ramus of the mandible and the masseter muscle is a series of spaces called the submasseteric spaces. These spaces are formed because the fibres of the masseter muscle have multiple insertions on to most of the lateral surface of the ramus.

Between the medial surface of the ramus of the mandible and the medial pterygoid muscle lies the pterygomandibular space.

Behind the ramus of the mandible is located the parotid space, in and around the parotid gland.

The parapharyngeal space is bounded by the superior constrictor of the pharynx and the medial surface of the medial pterygoid muscle. This space is restricted to the infratemporal region of the head and the suprahyoid region of the neck. It communicates with the retropharyngeal space, which itself extends into the retrovisceral space in the lower part of the neck.

The peritonsillar space lies around the palatine tonsil between the pillars of the fauces. It is part of the intrapharyngeal space and is bounded by the medial surface of the superior constrictor of the pharynx and its mucosa.

Most dental abscesses from lower teeth will drain either into the mouth lingually above the mylohyoid muscle (sublingual space) or into the vestibule (above the buccinator) and will have natural drainage. Where, for example, a cheek tooth drains below the buccinator (into the buccal space) or lingually below the mylohyoid (into the submandibular space, especially when involving the second and third mandibular molars), surgical intervention will be required to ensure drainage. As an example, direct spread may involve the submental space and the sublingual and submandibular spaces of both sides, giving rise to Ludwig's angina.

The teeth of the upper jaw have special relevance to ENT surgeons because of their potential close relationship to the maxillary air sinus. The root apices of the maxillary cheek teeth are close to and may even invaginate the maxillary sinus. The permanent tooth most commonly involved is the second molar, followed by the first molar. However, the premolars may also be involved as might the third molar. Following tooth extraction, resorption of alveolar bone and cavitation of the maxillary sinus may significantly increase. During removal of fractured root apices in this region, care must be taken to ensure the root fragment is not pushed into the sinus. Similarly, during root canal treatment, care must be taken not to push any filling material into the maxillary sinus. Routine X-rays may no longer be considered satisfactory in providing sufficient definition of the close relationship between the floor of the maxillary sinus and root apices and cone beam computed tomography may be necessary to provide extra detail (**Figure 41.16**). Due to the close anatomical relationship of the openings of the various air sinuses in the region of the middle meatus, infection of the maxillary sinus may spread to involve other sinuses and vice versa.

THE SALIVARY GLANDS

Salivary glands are compound, tubular, acinous, merocrine glands whose ducts open into the oral cavity. They secrete a fluid, the saliva that, among its many functions, aids in the mastication, digestion and deglutition of food.[8–10]

There are three pairs of major salivary glands: the parotid, the submandibular and the sublingual glands. Numerous minor salivary glands are also scattered throughout the oral mucosa.

Approximately 0.5 L of saliva is secreted per day. Salivary flow rates are approximately 0.3 mL/min when unstimulated, rising to 1.5–2 mL/min when stimulated. During sleep, salivary flow rate is negligible. In the unstimulated state, the parotid gland contributes approximately 20%, the submandibular gland approximately 65% and the sublingual and minor salivary glands the remainder. When stimulated, the parotid contribution rises to 50%.[11]

Parotid gland

The parotid gland is the largest salivary gland. It is a serous gland. The parotid gland is situated in front of the external ear on the face and consequently will not

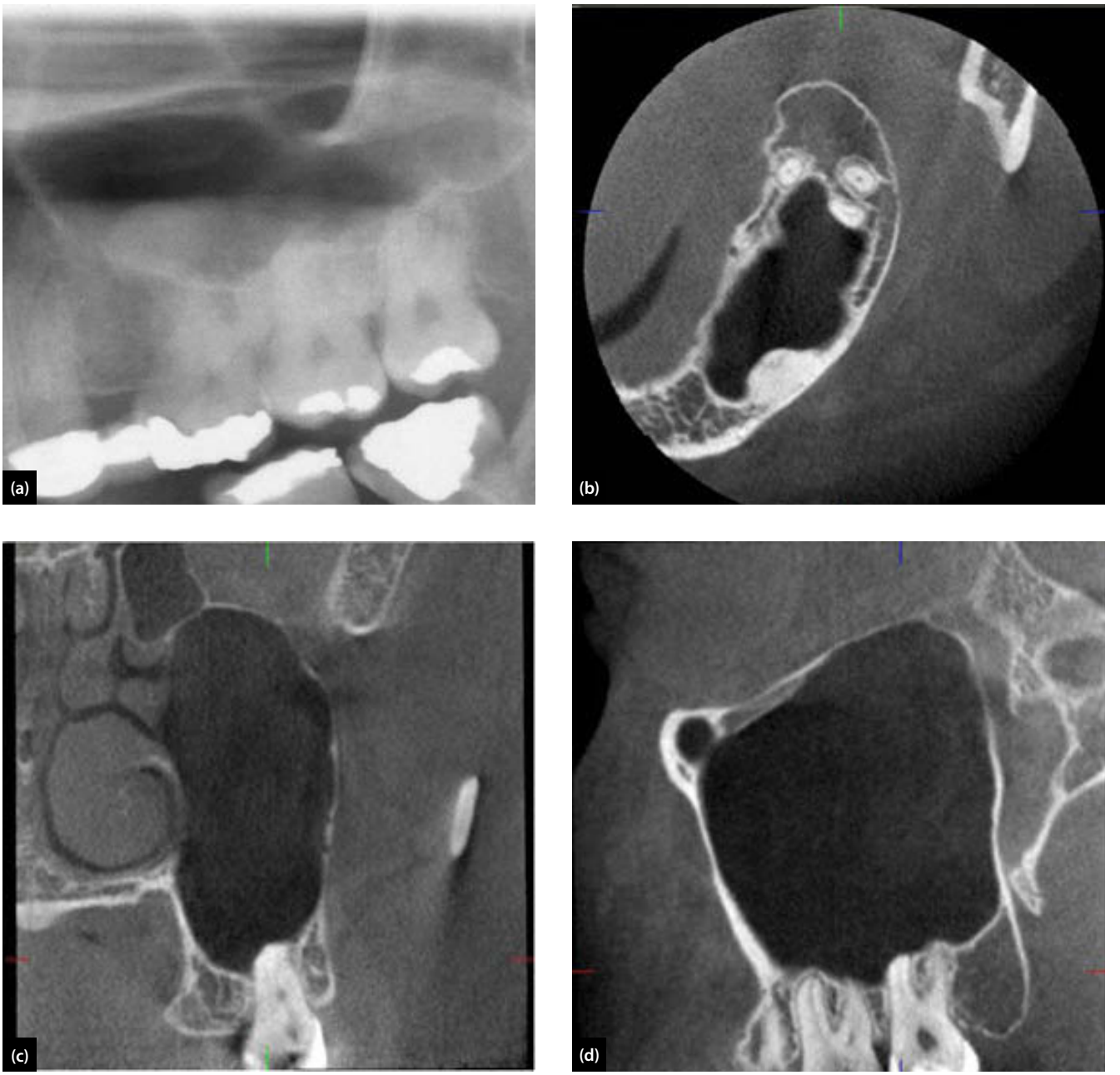


Figure 41.16 (a). Routine orthopantomograph showing roots of the left maxillary molars. The relationship of the root apices to the floor of the maxillary antrum is not clear. **(b,c,d)**. cone beam computed tomography of the same second and third maxillary molar teeth as in A, showing the precise relationship of the root apices to the floor of the maxillary sinus in three-dimensions. **(b)**. Axial image showing the palatal (P), distobuccal (DB) and mesiobuccal (MB) roots of the maxillary third molar **(c)**. Coronal image showing the mesiobuccal root (MB) of the maxillary third molar invaginating the floor of the maxillary simus. **(d)**. Sagittal image showing the mesiobuccal (MB) and distobuccal (DB) roots of the maxillary third molar invaginating the floor of the maxillary sinus. The roots of the adjacent maxillary second molar are also very close to the floor of the maxillary sinus, Courtesy of Dr J Davies.

be described further. The parotid duct runs through the cheek and drains into the mouth opposite the maxillary second permanent molar tooth. Its parasympathetic innervation is derived from the lesser petrosal branch of the glossopharyngeal nerve via the otic ganglion.

Submandibular gland

The submandibular gland is irregular in shape and approximately the size of a walnut. It consists of a larger superficial and a smaller deep part, continuous with each other around the posterior border of the mylohyoid muscle (see **Figure 41.7**). It is partially enclosed between two layers of deep cervical fascia extending from the greater cornu of the hyoid bone. It is a mixed, but predominantly serous, gland. The superficial part of the submandibular gland is situated in the digastric triangle. Above, it extends medial to the body of the mandible. Below, it usually overlaps the intermediate tendon of the digastric muscle and the insertion of the stylohyoid muscle.

The inferior surface, covered by skin, platysma and deep fascia, is crossed by the facial vein and the cervical branch of the facial nerve. The lateral surface is in relation with the submandibular fossa on the medial surface of the body of the mandible and the mandibular attachment of the medial pterygoid muscle. The medial (deep) surface is related anteriorly to the mylohyoid muscle and posteriorly to the styloglossus muscle. In its intermediate part, the medial surface is related to the hyoglossus muscle, separated from it by the styloglossus muscle, the lingual nerve, submandibular ganglion, hypoglossal nerve and deep lingual vein.

The deep part of the submandibular gland lies between the mylohyoid muscle inferolaterally and the hyoglossus and styloglossus muscles medially. It extends forwards to the posterior end of the sublingual gland (see **Figure 41.7**).

The submandibular duct is approximately 5 cm long and emerges from the medial surface of the superficial part of the gland behind the posterior border of the mylohyoid muscle. It passes through the deep part of the gland, runs between the sublingual gland and the genioglossus muscle and opens in the floor of the mouth on the summit of the sublingual papilla at the side of the frenulum of the tongue. On the hyoglossus muscle it is crossed laterally by the lingual nerve, some of whose terminal branches ascend on its medial side (see **Figures 41.7** and **41.8**).

The secretomotor supply to the submandibular gland is associated with the submandibular ganglion. This is a small, fusiform body that lies on the upper part of the hyoglossus muscle suspended from the lingual nerve. The motor, parasympathetic root conveys preganglionic fibres travelling in the facial, chorda tympani and lingual nerves (see **Figure 41.9**) to the ganglion, where they synapse. The postganglionic fibres are distributed to the submandibular and sublingual salivary glands.

Sublingual gland

The sublingual gland, the smallest of the main salivary glands, lies beneath the oral mucosa, which is raised as a sublingual fold (see **Figure 41.3**). The gland lies in contact with the sublingual fossa on the lingual aspect of the mandible, close to the mandibular symphysis. It is narrow, flat, shaped like an almond and weighs 3–4 g. The gland is seromucous (but predominantly mucous). Beneath the gland is the mylohyoid muscle, whilst behind it lies the deep part of the submandibular gland (see **Figure 41.7**). The genioglossus muscle lies medial to the sublingual gland, separated from it by the lingual nerve and submandibular duct. The sublingual gland has 8–20 excretory ducts. From the posterior part of the gland, smaller sublingual ducts mostly open separately on the summit of the sublingual fold. From the anterior part of the gland small rami sometimes form a major sublingual duct (Bartholin's duct), opening with or near to the orifice of the submandibular duct.

Minor salivary glands

The minor salivary glands of the mouth include the buccal, labial, lingual, palatal and palatoglossal glands. The buccal and labial glands contain both mucous and serous elements. The palatal glands are mucous glands. They are located in both the soft and hard palate. The anterior and posterior lingual glands are mainly mucous. The anterior glands are embedded within muscle near the ventral surface of the tongue and open by means of four or five ducts near the lingual frenum. The posterior glands are located in the root of the tongue. Around the circumvallate papillae are serous glands (of Von Ebner). The palatoglossal glands are mucous glands and are located around the pharyngeal isthmus.

TEMPOROMANDIBULAR JOINT

As the temporomandibular joint is closely related anatomically to the external acoustic meatus and clinical conditions of the joint may produce symptoms of pain that must be distinguished from those directly associated with the ear, the joint will be considered in this chapter.

The temporomandibular (craniomandibular) joint (TMJ) is a synovial joint. It is formed by the mandibular (glenoid) fossa articulating with the mandibular condyle. The TMJ has a number of unusual features:

1. The joint space is divided into two joint cavities (upper and lower) by an intra-articular disc.
2. The articular surfaces are not composed of hyaline cartilage but of fibrous tissue (reflecting the joint's intramembranous development).
3. A secondary condylar cartilage is present in the head of the condyle until adolescence.
4. Movements of the joint are influenced by the teeth.

The shape of the mandibular fossa does not conform exactly to the shape of the mandibular condyle and this may partly explain why the joint cavity is divided by an articular disc into upper and lower compartments (**Figure 41.17**).[6, 13] The TMJ allows both gliding (upper joint compartment) and hinge (lower joint compartment) movements.

The condyle joins the ramus through a thin bony projection termed the neck of the condyle, a frequent site for a fracture of the mandible. A small depression (the pterygoid fovea) situated on the anterior surface of the neck marks part of the attachment of the lateral pterygoid muscle. The articular surfaces of the condyle are the anterior and superior surfaces. During the period of growth up to early teens, a layer of hyaline cartilage (condylar cartilage) lies immediately beneath the fibrous articulating surface of the condyle.

The joint capsule

The capsule of the TMJ is attached above to the mandibular fossa, extending anteriorly to just in front of the crest of the articular eminence and posteriorly to the squamotympanic and petrotympanic fissures. Below, the capsule is attached to the neck of the condyle. Being a thin

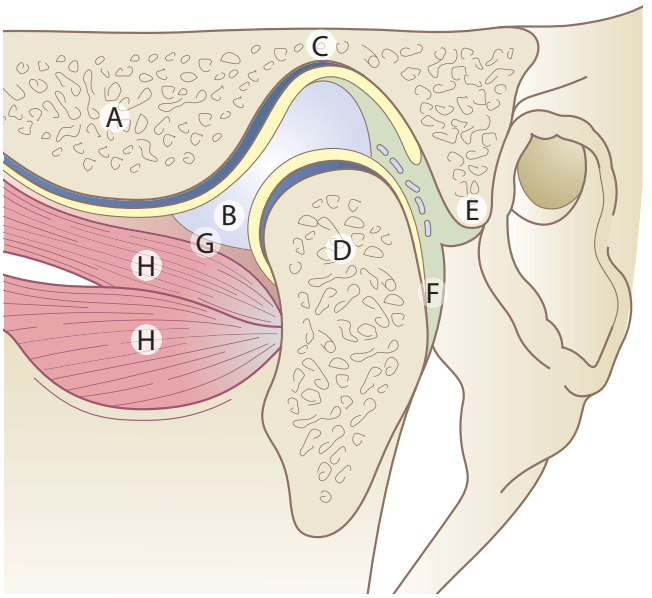


Figure 41.17 The temporomandibular joint showing the articular disc and attachments of the lateral pterygoid muscle. A, Articular eminence; B, articular disc; C, mandibular fossa; D, condyle; E, upper lamina (fibro-elastic); F, lower lamina (non-elastic); G, capsule of joint; H, lateral pterygoid muscle. Yellow layers indicate upper and lower joint cavities, black layers indicate upper and lower fibrous articular surfaces. Redrawn by permission from Ref. 12.

slack cuff, the capsule itself does not limit mandibular movements and is too weak to provide much support for the joint.

The inner surface of the fibrous capsule is lined by a synovial membrane that is reflected over the margins of the articular disc, but the membrane does not cover the articular surfaces of the joint. The synovial membrane secretes the synovial fluid, which occupies the joint cavities and lubricates the joint. Important components of the fluid are the proteoglycans. At rest, the hydrostatic pressure of the synovial fluid has been reported as being subatmospheric, but this is greatly elevated during mastication.[14, 15]

Articular disc

The articular disc (meniscus) is of a dense, fibrous consistency and is moulded to the bony joint surfaces above and below. Blood vessels are only evident at the periphery of the articular disc, the bulk of its central part being avascular. When viewed in sagittal section, the upper surface of the disc is concavo-convex anteroposteriorly and the lower surface is concave. Viewed superiorly, the articular disc is somewhat rectangular or oval in outline. The overall shape of the articular disc is thought to provide a self-centring mechanism, which automatically acts to maintain its correct relationship to the articular surface of the mandibular condyle during mandibular movements. Whereas some regard the functions of the articular disc as helping to spread the joint forces and to stabilize the condyle, others see its function as primarily destabilizing the condyle and permitting it to move more freely.[16]

The central (intermediate) zone of the disc is the thinnest and the collagen fibres are crimped, perhaps evidence that the disc is subjected to tensional, as well as compressional, forces.[17] The margin of the articular disc merges peripherally with the joint capsule. Anteriorly, fibrous bands connect the disc to the anterior margin of the articular eminence above, and to the anterior margin of the condyle below. Medially and laterally, the articular disc is attached to the joint capsule and, just below the medial and lateral poles of the condyle, by triangular zones of connective tissue. Posteriorly, the disc is attached to the capsule by a looser connective tissue, the retrodiscal tissue (pad) that has a bilaminar appearance. The superior lamina is loose and possesses numerous vascular elements and elastin fibres. It attaches to the anterior margin of the squamotympanic fissure. The inferior lamina is relatively avascular, less extensible (as it has few elastin fibres) and is attached to the posterior margin of the condyle. The volume of the retrodiscal tissue appears to increase four to five times as a result of venous engorgement as the jaw is opened and the condyle moves downwards and forwards. The return of the articular disc to its original position may possibly be aided by the elastic recoil of the superior lamella.

Numerous studies have been undertaken to determine the precise attachment of the lateral pterygoid muscle with respect to the articular disc in the hope of explaining any predisposition to TMJ syndrome. Variations in the attachment are seen. The findings indicate that, in the majority of articles (60%), fibres from the superior head of the lateral pterygoid muscle are described as gaining a direct attachment into the capsule of the joint and to the medial aspect of the anterior border of the articular disc (as well as to the condyle). In 30% of articles, only a few muscle fibres are described as inserting into the disc, while in the remaining 10% of articles the superior head of the lateral pterygoid muscle is attached only to the condyle.[18] Very rarely, some fibres from the inferior head of the lateral pterygoid may insert into the articular disc.

Considerable research has been undertaken on the activity of the lateral pterygoid muscle as it is believed by some that impaired activity of the muscle might predispose the joint to developing a pathology. It was originally thought that the two heads of the lateral pterygoid were reciprocal during opening and closing, the inferior head being active in opening the jaw, the superior head during closure, this view has now changed. The superior head has now been demonstrated to be active during opening and the two heads must be considered as acting together as one muscle with functional heterogeneity and with varying amounts of evenly graded activity throughout its range.[19]

Ligaments of the temporomandibular joint

The main ligament limiting lateral movement at the TMJ is the lateral ligament (temporomandibular ligament), which cannot be readily separated from the capsule. It runs

downwards and backwards from the articular tubercle (a bony protrusion on the lateral surface of the articular eminence) to the lateral surface and posterior border of the neck of the mandibular condyle.[19] To help resist posterior movement of the mandibular condyle, the lateral ligament is reinforced by a horizontal band of fibres running from the articular eminence to the lateral surface of the condyle. As there is little evidence of a medial ligament, medial displacement of the TMJ is likely to be prevented by the lateral ligament of the opposite side.

Accessory ligaments of the TMJ are the stylomandibular ligament, the sphenomandibular ligament and the pterygomandibular raphe. However, of these, the only one likely to have any significant influence upon mandibular movements is the sphenomandibular ligament.[20]

The stylomandibular ligament is merely a reinforced lamina of the deep cervical fascia that extends from the tip of the styloid process and from the stylohyoid ligament to the angle of the mandible.

The pterygomandibular raphe is a thin band of tendinous fibres passing between the hamulus of the medial pterygoid plate and the posterior end of the mylohyoid line of the mandible. It gives origin anteriorly to the buccinator muscle and posteriorly to the superior constrictor muscle.

The sphenomandibular ligament runs from the spine of the sphenoid bone to the lingula of the mandible. It represents the remnants of the perichondrium of the cartilage of the embryonic first branchial arch. The sphenomandibular ligament is slack when the jaws are closed, but during jaw movement becomes tense at about the time when the condyle has passed in front of the lateral ligament.[20]

In addition to the above, an additional ligament, the retinacular ligament, has recently been described. This ligament is said to originate from the articular eminence and insert into the fascia overlying the masseter muscle at the angle of the mandible. As the ligament is connected with the retrodiscal tissues, and contains an accompanying vein, it may function in maintaining blood circulation during masticatory jaw movements.[21]

Innervation and vasculature of the temporomandibular joint

Innervation for the joint is provided by the auriculotemporal, masseteric and deep temporal branches of the mandibular nerve. Of particular functional significance are the proprioceptive nerve endings important in the reflex control of mastication.

The vascular supply is derived from the superficial temporal artery and the maxillary artery (anterior tympanic and deep auricular branch). Other branches from neighbouring arteries may also contribute (e.g. deep temporal and transverse facial arteries).

Condylar cartilage

A secondary cartilage is present beneath the fibrous articular surface of the condyle until puberty. Unlike a primary cartilage, this secondary condylar cartilage has less extracellular matrix, the cartilage cells themselves do not undergo cell division and do not align themselves into columns. Although once thought to be a prime causative factor in controlling mandibular growth, the secondary condylar cartilage is now not thought to have any intrinsic growth potentiaton. The condylar cartilage disappears around the age of 16 years.

Clinical considerations of the temporomandibular joint

Estimates indicate that a considerable proportion of the population suffer in varying degrees from TMJ disorders. TMJ disorders are multifactorial in origin, although they may present with common symptoms such as pain in the jaw joint or face, clicking sounds in the joint and limited mouth opening.

Like other synovial joints, the TMJ is prone to inflammatory and degenerative conditions, such as rheumatoid and osteoarthritis. In these situations, damage to the articular surfaces will subject the articular disc to increased friction that may lead to degenerative changes within the disc. The intra-articular disc may gradually become displaced from its normal position between the articular surfaces. With the more usual anteromedial displacement, the posterior part of the disc may end up between the bony articular surfaces and be subjected to abnormal loading. The associated loss of structure may be accompanied by an invasion of blood vessels, with the disc eventually becoming perforated. The accompanying degenerative changes may also result in exposure of bone at the articular surfaces.

Inflammatory changes and increased permeability of the vessels of the synovial membrane may raise the intra-articular fluid pressure and change the composition of the synovial fluid. The synovial fluid in TMJ disorders may show an increased content in molecules such as proinflammatory cytokines (e.g. interleukin, tumour necrosis factor), matrix metalloproteinases and vascular endothelial growth factor. Irrigating and aspirating the joint (arthrocentesis) may reduce symptoms and improve mobility.

TMJ disorders are discussed in greater detail in Chapter 57, Temporomandibular joint disorders.

DEVELOPMENT OF THE FACE AND PALATE

As the neural plate of the embryo invaginates to form the neural tube, neural crest cells (ectomesenchyme) at the margins proliferate and migrate from this site to various parts of the body. There, interacting with the overlying epithelium (epithelial/mesenchymal interactions), the neural crest plays a significant role in normal development, contributing to many systems, such as the nervous system, soft and hard connective tissues. In addition, the cells play a major role in tooth development and give rise to melanocytes.

Development of face

In a 4-week-old embryo, the developing oral cavity (stomodeum) is present as a small, blind-ended pit bounded by five facial swellings (prominences) produced by proliferating zones of mesenchyme lying beneath the surface ectoderm. Much of the mesenchyme is derived from neural crest cells. The five facial swellings are the single frontonasal and the paired maxillary and mandibular processes (**Figure 41.18**). The centrally positioned frontonasal process lies above, the two maxillary processes are located at the sides and the two mandibular processes lie below the mouth. The maxillary and mandibular processes are derived from the first branchial arches. The facial processes are separated by grooves that, in the course of normal development, become flattened out by the proliferative and migratory activity of the underlying mesenchyme. Any disturbance in this process affecting, for example, the number, migration and subsequent differentiation (or apoptosis) and pattern formation of these cells can produce congenital abnormalities such as cleft lip and palate.

At this early stage of development, a membrane (the oropharyngeal membrane) separates the invagination representing the primitive oral cavity from the developing pharynx behind. The oropharyngeal membrane is bilaminar, being composed of an outer ectodermal layer and an inner endodermal layer. This membrane soon breaks down to establish continuity between the ectodermally lined oral cavity and the endodermally lined pharynx. Although not detectable in the adult, the demarcation zone between mucosa derived from ectoderm and endoderm corresponds to a region lying just behind the third permanent molar tooth.

In a 5-week-old embryo, localized thickenings of ectoderm on each side give rise to the optic and nasal placodes. These placodes will invaginate to form the lens of the eye and the olfactory epithelium, respectively. The nasal placodes sink into the underlying mesenchyme, forming two blind-ended nasal pits. Proliferation of mesenchyme from the frontonasal process around the openings of the nasal pits produces the medial and lateral nasal processes. The nasal pits continue to deepen until eventually they approach the roof of the primitive oral cavity, being partitioned from it by oronasal membranes (**Figure 41.19**). By the end of the fifth week, these membranes rupture to produce communications between the developing nasal and oral cavities.

In the 6-week-old embryo, the two mandibular processes fuse in the midline to form the tissues of the lower jaw. Rarely, persistence of a midline groove in this region

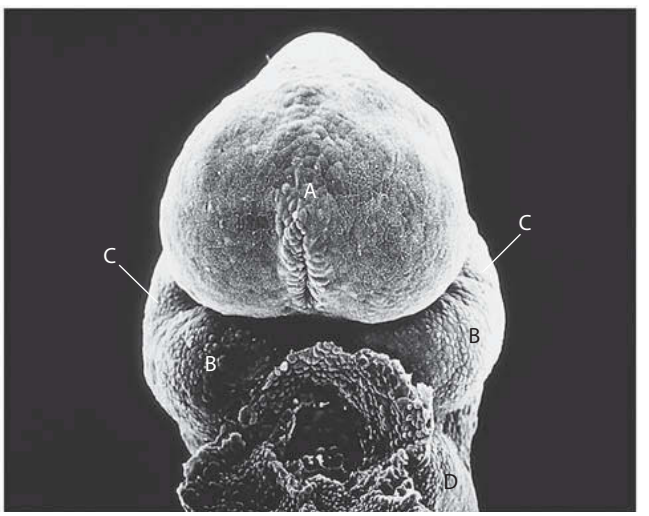
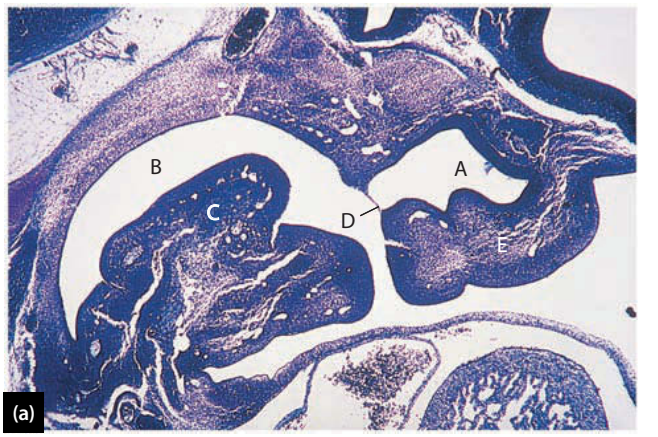


Figure 41.18 Scanning electron micrograph of the face at an equivalent 4-week stage (in the rat). Frontal aspect. A, Frontonasal process; B, mandibular processes; C, maxillary processes; D, pericardial swelling. Reprinted from Ref. 1 by permission from Elsevier.



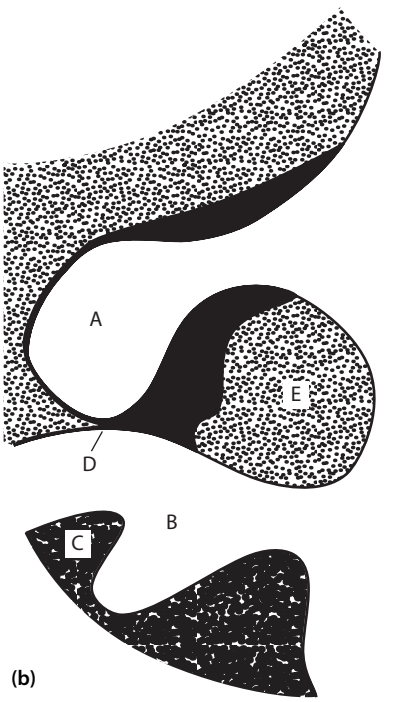


Figure 41.19 (a) Sagittal section through the developing nasal A and oral B cavities to C, developing tongue D, oronasal membrane; E, maxillary isthmus. Toluidine blue ×30. **(b)** Diagram with similar labelling. Reprinted from Ref. 1 by permission from Elsevier.

produces a mandibular cleft. The mandibular and maxillary processes meet at the angle of the mouth (labial commissure), thus defining its outline. Disturbances in this development may give rise to macrostomia (enlarged oral orifice) or microstomia (small oral orifice), or rarely to an astomia (lack of an oral orifice). From the corners of the mouth, the maxillary processes grow inwards beneath the lateral nasal processes and towards the medial nasal processes of the upper lip (**Figure 41.20**). An appreciation of this arrangement helps explain the occurrence of a unilateral or bilateral cleft lip (when the medial nasal and maxillary processes fail to merge successfully) and a median cleft (when the two median nasal processes fail to merge). The severity of a cleft may vary from a barely imperceptible groove to a complete cleft. Between the merging maxillary and the lateral nasal process lies the naso-optic furrow. From each furrow a solid ectodermal rod of cells sinks below the surface and canalizes to form the nasolacrimal duct. Persistence of the naso-optic furrow may produce an oblique facial cleft.

Two differing accounts have been given for the development of the upper lip. One interpretation is that the maxillary processes meet the medial nasal processes, the latter thus forming the middle third of the upper lip. This view is favoured by macroscopic observations of development. The alternative view states that the maxillary processes overgrow the medial nasal processes, merging in the midline to contribute all the tissue for the upper lip. This interpretation is based on the innervation of the fully formed upper lip (i.e. the infraorbital branch of the maxillary division of the trigeminal nerve), the maxillary processes being supplied by the maxillary nerve, the frontonasal process by the ophthalmic nerve. It is of interest to note that, in cases of bilateral cleft lip, the isolated median segment of the lip is innervated by the ophthalmic nerve, although this clearly is a pathological condition. At present, too little is known about the behaviour and any subsequent migration of the mesenchyme of the facial processes and the accompanying nerves after the initial fusion of the maxillary and medial nasal processes. The muscles of the lip, like the other facial muscles, are derived from the mesenchyme of the second branchial arch, and are therefore innervated by the facial nerve.

Fusion between the maxillary and medial nasal processes during the formation of the upper lip involves active epithelial filopodial and adhering interactions, as well as programmed cell death. Slight defects in growth and patterning of the facial mesenchyme or epithelial fusion result in cleft lip with or without cleft palate, the most common and disfiguring craniofacial birth defect. Recent studies of craniofacial development in animal models have identified components of several major signalling pathways, including Bmp, Fgf, Shh and Wnt signalling, that are critical for proper midfacial morphogenesis and/or lip fusion.

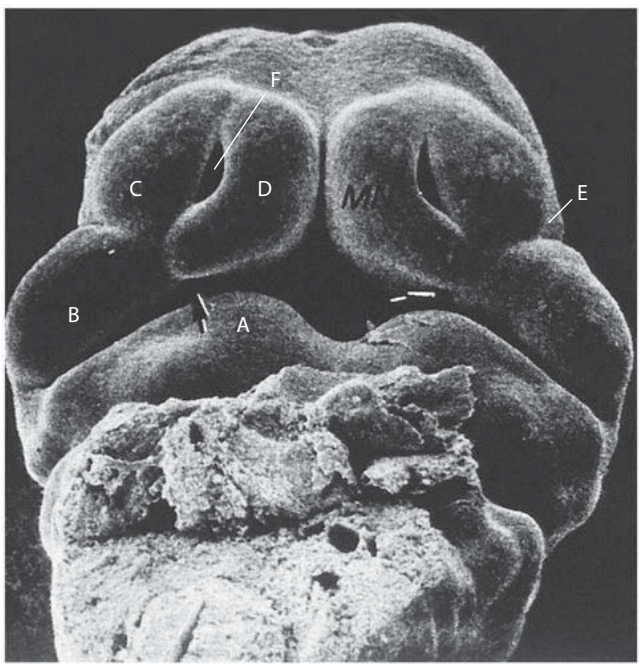


Figure 41.20 Scanning electron micrograph of developing rat upper jaw and lip at an equivalent stage to six weeks in the human showing the merging maxillary and medial nasal processes. A, Mandibular process; B, maxillary process; C, lateral nasal process; D, medial nasal process; E, naso-optic furrow; F, primitive nasal cavity. Reprinted from Ref. 1 by permission from Elsevier.

Development of the palate

As we have seen at 5 weeks of development, the nasal pit deepens and the nasal placode comes to lie in its roof where it will form the olfactory epithelium. The region of the frontonasal process lying between the two nasal pits forms the primary nasal septum, while the tissue beneath the pits and separating them from the stomodeum forms the primary palate. At this stage, the nasal pits are confined only to the anterior extremity of the future oral cavity, the large region behind at this stage forming a common oronasal cavity (**Figure 41.21a**). Subsequent development is designed to extend the primary nasal septum and primary palate backwards by means of a secondary nasal septum and secondary palate.

During the 6th week of development, a secondary nasal septum grows down from the roof of the stomodeum behind the primary nasal septum, thus dividing the nasal aspect of the common oronasal cavity into two. In addition, a lateral palatal shelf grows out from each maxillary process but, due to the comparatively large size of the developing tongue, is prevented from growing horizontally and becomes oriented more vertically (**Figures 41.21b** and **41.22**).

During the 8th week of development, the tongue 'drops' and the vertically inclined palatal shelves can now occupy a horizontal position (**Figures 41.21c** and **41.23**). The reason for the displacement of the tongue is not known. As the tongue is attached to the mandible, it has been suggested that the descent of the tongue is related to mandibular growth. Conversely, reflex movements of the tongue and/or a change in its shape may be implicated. On becoming horizontal, the palatal shelves contact each other

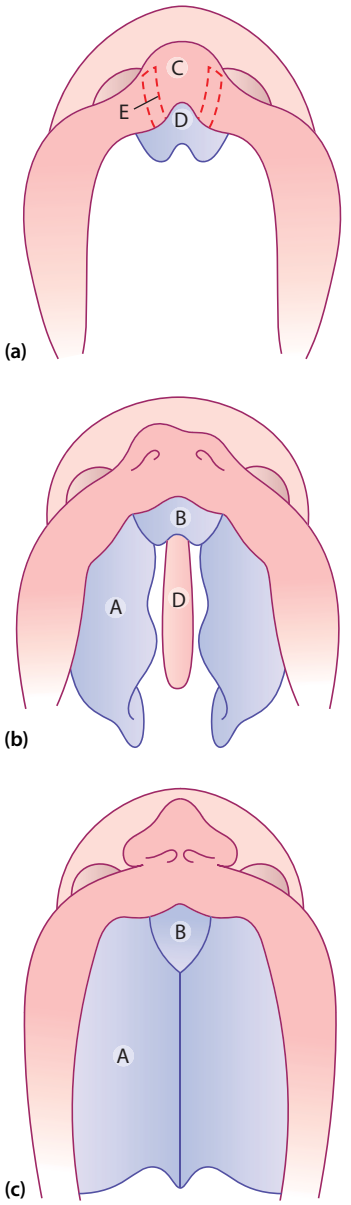


Figure 41.21 Diagram showing the development of the palate (a). By 6th week of intrauterine life; **(b)** during 6th week of intrauterine life and **(c)**. At 9th week of intrauterine life. A, lateral palatal shelves of secondary palate; B, primary palate; C, primary nasal septum; D, secondary nasal septum; E, primitive nasal cavities.

(and the secondary nasal septum) in the midline to form the secondary palate. The shelves contact the primary palate anteriorly so that the oral and nasal cavities become completely separated from each other. After shelf contact, the medial edge epithelia of the two shelves fuse to form a midline epithelial seam. Subsequently, this seam (together with the epithelium separating the palatal shelves from the secondary nasal septum) degenerates, allowing continuity of mesenchyme to be established across the now intact and horizontal secondary palate. Fusion of the palatal processes is complete by the 12th week of development. Behind the secondary nasal septum, the palatal shelves fuse to form the soft palate and uvula.

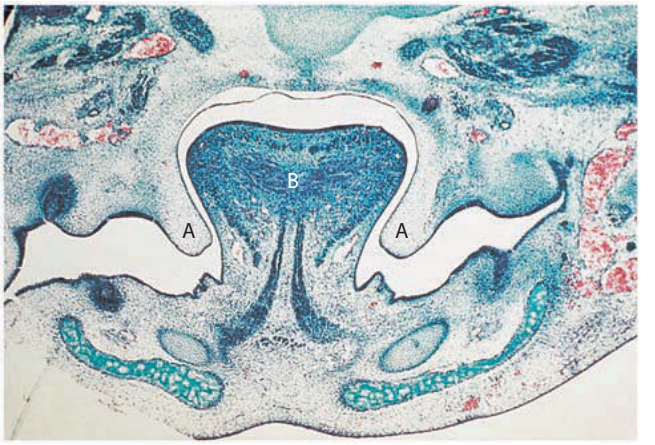


Figure 41.22 Coronal section through the head at an equivalent stage of seven weeks intrauterine development in the human showing the vertically inclined palatal shelves (A). B, Developing tongue. Masson's trichrome ×30. Reprinted from Ref. 1 by permission from Elsevier.

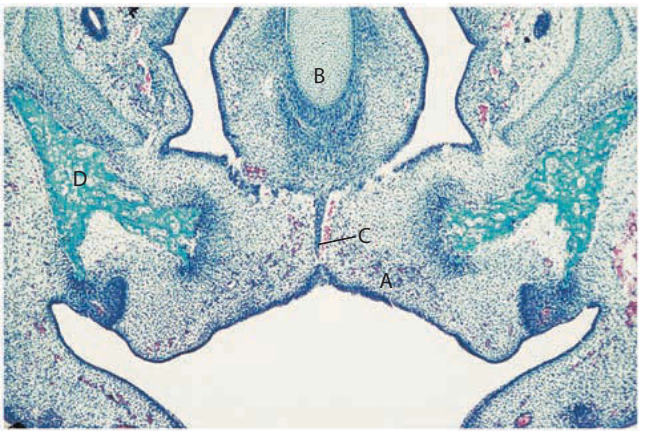


Figure 41.23 Coronal section through developing oro-nasal regions following contact of the palatal shelves (A) and secondary nasal septum (B). C, Midline epithelial seam; D, developing bone of maxilla. Masson's trichrome ×30. Reprinted from Ref. 1 by permission from Elsevier.

The hard palate ossifies intramembranously from four centres of ossification, one in each developing maxilla and one in each developing palatine bone. The maxillary ossification centre lies above the developing deciduous canine tooth germ and appears in the 8th week of development. The centre of ossification for the palatine bone is situated in the region forming the future perpendicular plate and appears in the 8th week of development. Incomplete ossification of the palate from these centres defines the median and transverse palatine sutures. There does not appear to be a separate centre of ossification for the primary palate in man (in other species there is such a centre, forming a separate 'premaxilla').

The muscles of the palate are derived from the lower branchial arches, hence their nerve supply by the pharyngeal plexus. However, tensor veli palatini develops from the first branchial arch, explaining its innervation by the mandibular nerve.

As is evident from the description above, palate formation is a complicated process. The palatal shelves must grow to the appropriate size; the palatal shelves must elevate at the appropriate time on both sides; the medial edge epithelia of the palatal shelves must adhere to form a midline epithelial seam: the midline epithelial seam must degenerate to allow for the establishment of mesenchymal continuity across the midline. Any interference or mistiming of these processes may contribute towards the formation of a cleft palate. Clefts of the palate, like those of the lip, are multifactorial malformations, involving both genetic (polygenic) and environmental factors. Recent research on palatogenesis has concentrated on two main events: palatal shelf elevation and the initial stage of fusion of the shelves.

PALATAL SHELF ELEVATION

This process, during which the palatal shelves move from the vertical to the horizontal position, is thought to occur very rapidly (in terms of minutes and hours rather than days). Although it was once thought that extrinsic forces might be responsible (e.g. forces derived from the tongue or jaw movements), recent research has primarily focused on the search for a force intrinsic to the palatal shelf. Systems which have at one time or another been implicated include differential mitosis, contraction of connective tissue elements such as collagen or mesenchymal cells, changes in vascularity or tissue-fluid pressures. Particular attention has focused on the proposition that the intrinsic shelf elevation force might develop as a result of hydration of ground substance components (principally hyaluronan) in the shelf mesenchyme.[22] In this context, hyaluronan is a highly electrostatically charged, open coil molecule that is capable of binding up to ten times its own weight in water. In support of the possible importance of hyaluronan in palatogenesis, research using organ culture systems have shown that the presence of agents either leading to an alteration in hyaluronan content or size, or that disrupt glycosaminoglycan substitution on proteoglycans, or that alter the balance of matrix molecules secreted via the Golgi complex and hyaluronan produced at the cell surface, all detrimentally affect normal palatogenesis.[1] In addition to hyaluronan, however, other matrix components (including proteoglycans) may also be important during shelf elevation.

FUSION OF THE PALATAL SHELVES

Following palatal shelf elevation, contact is made initially in the middle third of the palate and then extends both anteriorly and posteriorly. The two adjacent medial edge epithelium contact each other and adhere by means of a 'sticky' glycoprotein coating their surfaces. In addition, the epithelial cells develop desmosomes that form a medial epithelial seam. The adherence of the medial edge epithelia is site-specific as palatal epithelia will not fuse with epithelia from other sites (e.g. the tongue).[22]

For normal palatogenesis to proceed, the epithelial seam must be removed for consolidation of mesenchymal tissues across the midline. The signals that are responsible for such a breakdown are not yet fully understood. As a breakdown of medial edge epithelium occurs in single isolated palatal shelves, the process does not depend specifically upon shelf contact.

Factors that may contribute to thinning and then removing the epithelial seam include: growth of the palate (in terms of oronasal height) and epithelial cell migration from the region of the seam on to the oral and nasal aspects of the palate; programmed epithelial cell death (apoptosis); migration of epithelial cells from the epithelial seam into the palatal shelf mesenchyme and their subsequent differentiation into mesenchymal cells (epithelial/mesenchymal transformation).[23] As in other systems, it is thought that signals (e.g. growth factors such as epidermal growth factor and transforming growth factors) emanating from the underlying mesenchyme are ultimately responsible for controlling epithelial degeneration.

CLINICAL AND AETIOLOGICAL CONSIDERATIONS

Malformations of palatogenesis may result in the appearance of clefts. The mildest form of cleft is that affecting the uvula, such a disturbance occurring relatively late in the process of palatal fusion. Disturbances occurring during the early phases of palatal fusion can result in a more extensive cleft involving most of the secondary palate. Should the cleft involve the primary palate, it may extend to the right and/or left of the incisive foramen to include the alveolus, passing between the lateral incisor and canine teeth. Cleft palate may be associated with cleft lip, though the two conditions are independently determined. Dental malformations are commonly associated with a cleft involving the alveolus. A submucous cleft describes a condition where the palatal mucosa is intact, but the bone/musculature of the palate is deficient beneath the mucosa.

As with other situations of epithelial mesenchymal interactions, large numbers of genes, growth factors and their receptors, and transcription factor are involved to ensure that palatal development proceeds normally. These factors have been mapped and show differences at different stages of palatal development, some being more important at the early stages in palate formation, others being more involved at later stages. Their importance in palate development has been shown by experimental manipulation, when their inactivation has been associated with palatal cleft formation. In the early stages of epithelial-mesenchymal interactions, Shh, Fgf10 and Bmp2 and Bmp4 are especially important, as is the orderly release of matrix metalloproteinases (such as those associated with the degradation of versican). During palatal fusion, TGF beta has a prominent role.

With growth of the palatal shelves, there is considerable heterogeneity along the anteroposterior and mediolateral axes of molecules such as Shh, Bmp4, Msx1, Osr1, Barx1. However, the biochemical changes produced by the particular genes, growth factors and signalling molecules are poorly understood.

KEY POINTS

- A detailed knowledge of the anatomy of the mouth and dentition is mandatory for all head and neck surgeons operating in this area.
- For the general ENT surgeon, the anatomy of:
  - **the floor of mouth** is important when dealing with submandibular duct pathology or submandibular duct rerouting, tongue tie, treatment of a ranula and biopsying suspicious lesions;
  - **the buccal mucosa** is important when dealing with parotid duct pathology and biopsying suspicious lesions;
  - **the hard palate** is important when biopsying suspicious lesions;
  - **the soft palate** is important for understanding Eustachian tube pathology, palatal surgery for snoring, and for biopsying suspicious lesions;
  - **the palatine tonsil and lateral pharyngeal wall** are important for tonsillectomy and management of peritonsillar and parapharyngeal abscesses as well as biopsy of suspicious lesions;
  - **the tongue** is important when assessing neurological function after suspected hypoglossal nerve damage or chorda tympani loss, as well as for biopsy of suspicious lesions;
  - **the salivary glands** is important for understanding the principles of parotidectomy and submandibular gland excision;
  - **the temporomandibular joint** is important because of its close relationships to the external ear canal.

For the general ENT surgeon, understanding the development of the face and palate is helpful in understanding a wide range of congenital head and neck abnormalities and cleft palate pathologies in particular.

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CHAPTER 42

BENIGN ORAL AND DENTAL DISEASE

Konrad S. Staines and Alexander Crighton

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SEARCH STRATEGY

Data in this chapter may be updated with a search using the following keywords: dental caries, dental plaque, saliva, pulpitis, apical periodontitis, acute dentoalveolar abscess, pericoronitis, periodontal disease, gingivitis, herpetic oral ulceration, aphthous or aphthous-like ulceration and acute ulcerative (necrotizing) gingivitis, dental trauma, cleft lip and palate, alveolar osteitis, cysts of the jaw, ameloblastoma, oral mucosa, oral mucosa infections, herpes virus, oral candidiasis, aphthous ulcer, lichen planus, pemphigus, pemphigoid, graft versus host, orofacial pain, trigeminal neuralgia, cluster headache and temporomandibular disorders.

COMMON DISORDERS AFFECTING THE TEETH AND PERIDONTIUM

Dental caries

Dental caries is a dynamic, multifactorial, bacterial disease of teeth. The initial stage in dental caries is termed the initial enamel lesion. This typically arises at sites where dental plaque (a microbial biofilm adherent to tooth tissues) is persistent. The underlying process in the initial stages involves acid dissolution of calcified dental tissue creating a dynamic imbalance between demineralization and remineralization in favour of the former.

The pathophysiology of dental caries can be described in terms of the interplay of four factors: dental plaque, dental tissues, saliva and the substrate (**Table 42.1**).

Bacteria within dental plaque, most notably but not exclusively *Streptococcus mutans*, will metabolize substrates generating acid by-products at the plaque–enamel interface. A dynamic process with localized demineralization of the adjacent dental tissues countered by attempts at remineralization driven through saliva, will determine whether caries will develop. Dental plaque creates a microenvironment favourable to demineralization where the protective buffering and remineralization properties of saliva are accordingly diminished. The initial stage of

TABLE 42.1 Factors involved in the development of dental caries

Factor	Action
Salivary factors	Saliva has important cleansing, antibacterial and remineralization functions.
Dental plaque factors	Dental plaque is a microbial biofilm adherent to tooth tissues. Bacteria within plaque, most notably but not exclusively S. mutans, ferment carbohydrate substrates, producing acids that can potentially result in localized demineralization of the adjacent dental tissues. Dental plaque creates a microenvironment favourable to demineralization where the protective buffering and remineralization properties of saliva are accordingly diminished.
Substrate factors	Substrates that can utilized by plaque microorganisms to produce acid are considered cariogenic. Refined carbohydrates especially containing sucrose are examples of such substrates. However, naturally occurring substrates such as those found in fruit are also cariogenic.
Dental factors	Risk factors with regard to dental anatomy are those that favour accumulation of plaque and a favourable environment for caries formation. Examples of such factors include narrow fissures, pits, inadequate interdental contact points that allow food impaction, inadequate dental restoration margins.

dental caries involves the alteration of the enamel surface with acid permeating alongside the enamel prism sheaths causing localized enamel dissolution. This initial stage (with no cavitation or dentine involvement) is considered reversible and amenable to focused preventative treatment.

Should enamel caries progress, eventually, the enamel dentine junction is reached with the ultimate persistence of this process leading to cavitation. Caries may progress involving dentine acid dissolution, proteolysis and bacterial invasion of the dentinal tubules. Once the dental pulp is reached, infection and inflammation of the pulp (pulpitis) will follow.

The clinical diagnosis of caries involves detection and evaluation of the severity of the lesion through clinical examination (predominantly visual and tactile inspection using blunt dental probes) coupled with dental radiographic examination.

Operative treatment of dental caries is required as soon as there is surface cavitation with dentine involvement. The operative treatment of dental caries involves removal of carious tissue and restoring tooth integrity with a restoration. The restoration's function is to restore anatomy and prevent ingress of microorganisms into the restored cavity. Such ingress may, in the presence of other cariogenic factors described above, lead to recurrent caries around the restoration.

Non-carious tooth surface loss (tooth wear)

Tooth wear develops secondary to mechanisms that can be grouped as erosion, attrition, and abrasion occurring independently or in combination. An example of a common exacerbating factor is hyposalivation. The potential consequences of long-standing tooth wear include hypersensitivity secondary to dentine exposure, reduced masticatory function and poor dental aesthetics.

EROSION

Erosion can be defined as the non-plaque mediated chemical dissolution of tooth tissue.

This acid dissolution may be secondary to intrinsically derived acid such as the reflux of gastric acid in gastroesophageal reflux disease or through externally derived acids, with dietary consumption of acid food and drink being the most common cause. Predisposing factors such as hyposalivation may predispose to erosion-mediated tooth wear. Erosion may be a contributing factor to both attrition and abrasion secondary to 'softening up' of the calcified dental tissues.

ATTRITION

Attrition is tooth wear secondary to non-masticatory tooth-to-tooth contact. Bruxist clenching may predispose towards attrition.

ABRASION

Abrasion is tooth wear secondary to friction of exogenous material against the tooth surface. Abrasion may be caused by a variety of mechanisms with an appropriate example being overzealous toothbrushing.

Dental infections

The most common dental infections for which patients seek emergency dental care are pulpitis and apical periodontitis (periapical abscess), pericoronitis and periodontal abscess.

PULPITIS AND APICAL PERIODONTITIS

Pulpitis (dental pulp inflammation) occurs most commonly secondary to microbial infection involving a carious lesion. Less common pathways of infection are through a tooth fracture or in a retrograde manner through the apical foramen. Pulpitis is characterized by inflammation within the confines of the pulp chamber resulting in pressure causing occlusion of the blood vessels and necrosis of the pulp tissue. The pain changes from pain exacerbated by thermal stimuli in reversible pulpitis to a dull, throbbing, persistent poorly localized pain of spontaneous onset in irreversible pulpitis. Ultimately, progressive infection of the pulp chamber is followed by an anaerobic bacterial biofilm colonizing the walls of the necrotic root canals leading to asymptomatic necrosis or acute inflammation. The involvement of the periapical tissues via the apical foramen may elicit an acute inflammatory host response resulting in acute periodontitis. Symptoms indicating the development of apical periodontitis are the development of tenderness on application of pressure of the involved tooth. Dentists typically use the end of a dental mirror handle to tap on the tooth to elicit this. Treatment of pulpitis and apical periodontitis is through root canal treatment or dental extraction. Systemic antibiotics are not routinely prescribed.

Further spread of infection into the periapical tissues and formation of an acute dentoalveolar abscess is accompanied by pain, swelling, erythema and suppuration usually localized to the affected tooth. Surgical treatment is the management of choice for most dental abscesses by drainage of pus and elimination of the source of infection typically through root canal treatment or extraction of the tooth. Antimicrobial use should be mainly limited to spreading and severe infections which are still a cause of hospital admissions.

The host response to involvement of the periapical tissues via the apical foramen is predominantly mediated by T cells and macrophages, leading to a chronic periapical granuloma rather than an acute apical periodontitis. This is typically asymptomatic but may eventually be visible on radiographic examination of the apex of the tooth as a well-circumscribed radiolucency.

PERICORONITIS

Pericoronitis is an acute localized infection which develops around partially erupted teeth, with the most common site being around a partially erupted, impacted wisdom tooth. Presentation is with symptoms of pain aggravated by jaw movement and mastication, trismus and halitosis. On examination an inflamed operculum (gum flap) is invariably present around the affected tooth, associated with localized facial swelling, regional lymphadenopathy and inability to open the jaw to the usual range of movement.

Initial treatment may be limited to irrigation under the operculum with an appropriate topical preparation such as chlorhexidine 0.2%. Indications for systemic antimicrobial treatment include the presence of regional lymphadenopathy, trismus or spreading infection. As gram negative anaerobes are predominantly implicated in pericoronitis, metronidazole is often prescribed.

Periodontal disease (plaque related gingivitis and periodontitis)

The gingivae and the periodontium may become inflamed secondary to a variety of pathological causes ranging from autoimmune to infectious causes (**Figure 42.1**). The generic terms gingivitis and periodontitis are usually applied to plaque-related inflammation of these tissues. The aetiology of chronic adult periodontal disease is multi-factorial, involving interaction between dental plaque, genetic and environmental risk factors. Dental plaque differing in microbial composition, forms above (supra-) and below (sub-) the gingival margin. Periodontitis develops when the plaque-related gingivitis results in an increase in depth of the gingival sulcus by mechanisms involving apical migration of the gingival attachment to the tooth root surface, loss of connective tissue attachment and alveolar bone loss. Examples of clinical parameters used by dental surgeons to assess periodontal disease include placing a periodontal probe in the gingival sulcus, measuring pocket depth which allows an indication of periodontal attachment loss. Bleeding on placement of the periodontal probe tip into the gingival sulcus or periodontal pocket reflects the presence of active gingival inflammation (**Table 42.2**). There has been significant research into the aetiology and association between periodontal disease and systemic diseases such as diabetes mellitus and atherosclerotic vascular disease.

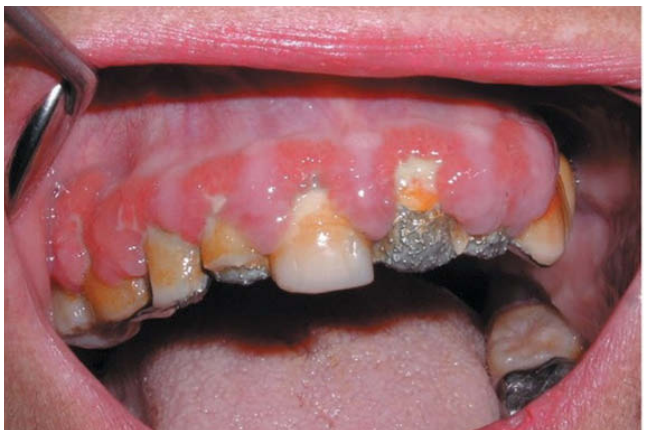

Figure 42.1 Chronic periodontitis.

TABLE 42.2 Causes of gingival bleeding

Local	Systemic
Chronic gingivitis	Any condition causing exacerbation of gingivitis (e.g. pregnancy)
Chronic periodontitis	Leukaemia
Acute necrotizing gingivitis	Human immunodeficiency virus infection
Angioma/telangiectasia	Other causes of purpura
	Clotting defects
	Drugs, e.g. anticoagulants
	Scurvy

GINGIVAL PIGMENTATION

Gingival pigmentation is common in dark-skinned races (**Figure 42.2**). Other common causes include amalgam tattoo and melanotic macules. Smoking, tobacco and betel chewing, and drugs such as hydroxycholoroquine and minocycline may also cause hyperpigmentation. Other causes are listed in **Table 42.3**. See also 'Changes in mucosal colour' below.

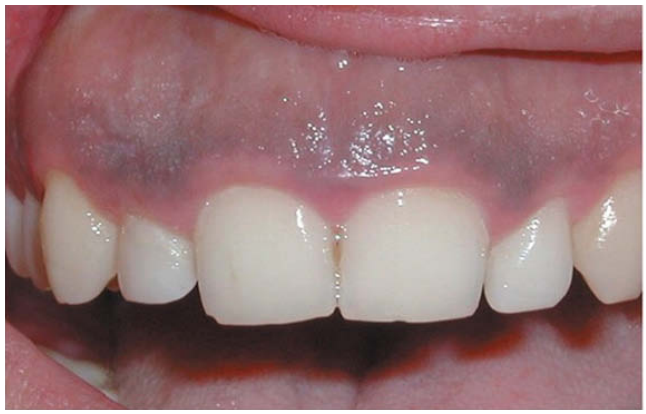

Figure 42.2 Gingival racial pigmentation.

TABLE 42.3 Causes of oral hyperpigmentation

Localized pigmentations	Generalized
Kaposi's sarcoma	Addison's disease
Malignant melanoma	Drugs, e.g. phenothiazines, antimalarials, minocycline, contraceptives
Melanotic macules	Ectopic ACTH (e.g. bronchogenic carcinoma)
Naevi	Heavy metals
Syndromes:	Syndromes:
Albright	Complex of myxomas, spotty pigmentation and endocrine overactivity
Laugier–Hunziker	Malignant acanthosis nigricans
Peutz–Jegher	Racial
Tattoos (amalgam or graphite)	Localized irritation, e.g. smoking
	Other rare causes, e.g. haemochromatosis, generalized neurofibromatosis, incontinentia pigmenti

GINGIVAL REDNESS

Chronic gingivitis is the usual cause of gingival redness and is usually restricted to the gingival margins and interdental papillae. More widespread gingival erythema in children is usually caused by herpetic stomatitis but, in adults, desquamative gingivitis (typically seen in lichen planus or pemphigoid) or occasionally allergic responses are responsible.

Localized red areas may represent erythroplasia, carcinoma, Kaposi's sarcoma, candidiasis, lichen planus or lupus erythematosus.

Telangiectasia may be a manifestation of hereditary haemorrhagic telangiectasia, primary biliary cirrhosis, systemic sclerosis, or may follow radiotherapy. Haemangiomas are usually isolated but may occasionally be part of a syndrome.

GINGIVAL SWELLINGS

Localized gingival swellings (epulides) may be of local aetiology (irritation) or can be manifestations of pregnancy, a neoplasm or systemic disease (**Table 42.4**). Generalized gingival swelling is most commonly seen in chronic gingivitis, or caused by drugs such as phenytoin, cyclosporin and calcium channel blockers (**Figure 42.3**) and is occasionally hereditary (hereditary gingival fibromatosis). Gingival swelling may also be seen in herpetic stomatitis, leukaemia, Crohn's disease (CD), orofacial granulomatosis, sarcoidosis, amyloidosis, scurvy and other disorders.

TABLE 42.4 Causes of gingival swelling

Generalized	Localized
Local	
Chronic gingivitis	Abscesses
Hyperplastic gingivitis due to mouth breathing	Cysts
	Pyogenic granuloma
	Neoplasms and warts (various)
Systemic	
Hereditary gingival fibromatosis and associated syndromes	Pregnancy
Drugs: Phenytoin Cyclosporin Calcium-channel blockers	Sarcoidosis
	Orofacial granulomatosis
	Crohn's disease
	Wegener's granulomatosis
Pregnancy	Amyloidosis
Sarcoidosis	Neoplasms (various)
Orofacial granulomatosis	
Crohn's disease	
Leukaemia	
Wegener's granulomatosis	
Scurvy	

GINGIVAL ULCERS

Neoplasms, herpetic oral ulceration, aphthous or aphthous-like ulceration, acute ulcerative (necrotizing) gingivitis (AUG) and other bacterial infections (e.g. syphilis, tuberculosis) are some of the conditions that cause gingival ulceration.

Dental trauma

Injury to the front teeth is especially common in, but not limited to, childhood. If a permanent incisor is avulsed then reimplantation as soon as possible is advisable. The tooth can be stored in a suitable medium such as milk pending reimplantation. If the deciduous tooth is avulsed then this should not be reimplanted. Fractures of the crown of the tooth should be attended to by a dentist as quickly as possible. If the fractured fragment can be identified it can be reattached to the tooth rather than a restorative filling material being placed. If there is any soft-tissue injury and a missing tooth fragment, the wound should be explored for the fragment before closure. Dental trauma can be a presentation of non-accidental injury in a child and this, together with the pattern of soft-tissue injury and other points from the history should remind the practitioner to consider this aetiology.

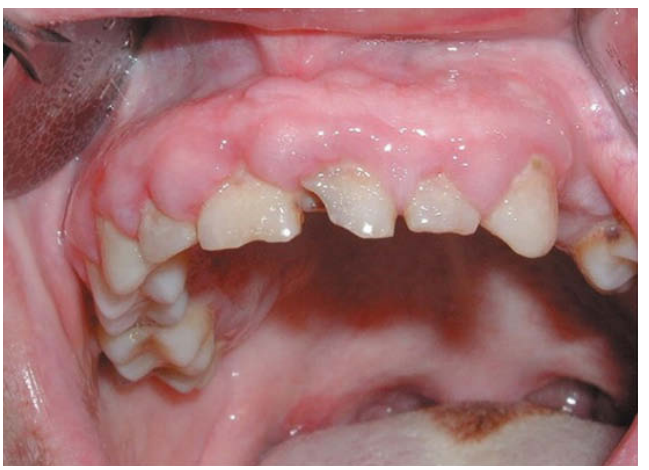

Figure 42.3 Drug-induced gingival swelling.

DEVELOPMENTAL DISORDERS OF TEETH

Abnormalities of tooth development and eruption may occur either as isolated defects or as part of a wider developmental disorder. Cleft lip and palate is an example of a disorder that may affect both tooth development and eruption. A discussion of other syndromes with associated craniofacial deformity and dental developmental disorders is outwith the scope of this chapter and is discussed in Volume 2, Chapter 6, The child with a syndrome. The effect of trauma may range from root dilaceration of a developing tooth or temporomandibular joint (TMJ) injury.

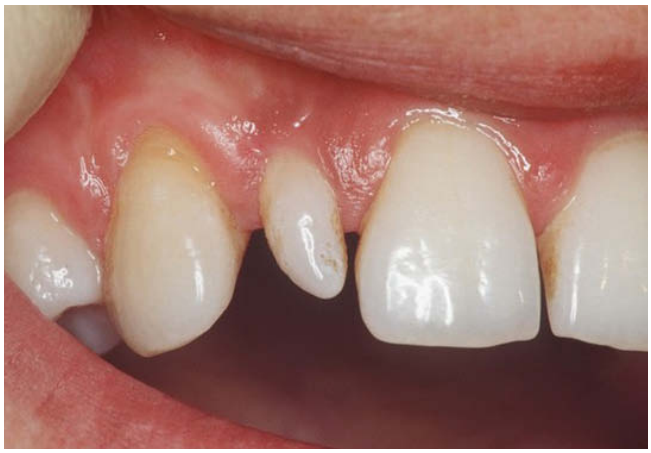

Figure 42.4 Peg-shaped lateral incisor.

Commonly the last tooth in each dental series may be missing or malformed, more commonly in the adult rather than the primary dentition. This is most often seen by the absence of the third molar tooth, followed by the lateral incisor and finally the second premolar. Multiple missing teeth is termed 'hypodontia' and requires a specialist assessment to plan for a functioning adult dentition. The commonest malformed tooth visible is the upper lateral incisor which is termed a 'peg' lateral incisor (**Figure 42.4**). Adhesive dental restorations, orthodontic tooth movement and dental implants have radically changed the outlook for patients with dental anomalies.

Systemic factors such as hypothyroidism may impact the developing dentition and result in delayed dental eruption. Drugs such as cytotoxic medication may result in delayed eruption.

Discoloured teeth

Teeth most commonly become discoloured through habits such as tobacco use, drinking tea, coffee and red wine (**Table 42.5**). It is important to consider iatrogenic causes of discolouration of teeth such as administration of tetracyclines to a child under 12 years of age or to a pregnant or lactating mother (**Figure 42.5**). Excess systemic fluoride intake in the developing dentition may cause a range of defects from white specks to brownish discolouration and surface irregularities (fluorosis). Chlorhexidine mouthwash especially when used for more than a week can cause discolouration of teeth and dental composite restorations.

Mobile teeth

Causes of early tooth loosening and loss are given in **Table 42.6**. The most common reason for tooth mobility is advanced periodontal attachment loss secondary to chronic adult periodontal disease. When trauma causes mobility, this will be evident from the history. It is important to be aware that in rare cases, malignancy may result in loosening of teeth. Rare systemic disease such as Langerhans cell histiocytosis may also result in localized periodontal attachment loss and tooth mobility.

TABLE 42.5 Causes of discolouration of teeth

Extrinsic	Intrinsic
Poor oral hygiene	Trauma
Beverages/food	Caries
Drugs, e.g. iron, chlorhexidine	Restorative materials, e.g. amalgam
Habits, e.g. smoking or betel chewing	Pink spot (internal resorption)
	Drugs — mainly tetracyclines
	Fluorosis
	Dentinogenesis imperfecta
	Amelogenesis imperfecta
	Porphyria
	Jaundice in neonate or infant

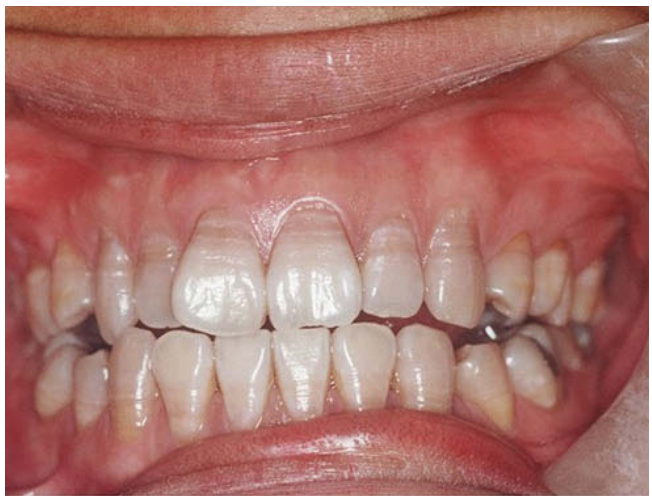

Figure 42.5 Intrinsic dental staining.

TABLE 42.6 Pathological causes of loosening and early loss of the teeth

Local causes	Systemic causes	Others
Trauma	Disorders with some immune deficit	Acrodynia
Periodontitis	Down syndrome	Neoplasms
	Diabetes mellitus	Eosinophilic granuloma
	Leukopenia or leukocyte defects	
	HIV disease	
	Juvenile periodontitis	
	Rapidly progressive periodontitis	
	Papillon–Lefèvre syndrome	
	Hypophosphatasia	
	Ehlers–Danlos syndrome (type VIII)	

Non-neoplastic lesions of the jaws

VARIATIONS OF NORMAL ANATOMY

Bony exostoses (tori) are commonly encountered on clinical examination of the oral cavity. Maxillary tori may be noted of the buccal and labial aspects of the alveolus or in the midline of the palate. Mandibular tori are typically present on the lingual aspect of the premolar regions. The presence of multiple tori within the oral cavity especially if associated with extraoral exostoses may raise a clinical suspicion of syndromes such as Gardner syndrome.

DEVELOPMENTAL BONE DISEASE OF THE JAWS

Osteogenesis imperfecta

Osteogenesis imperfecta (OI) is an autosomal dominant disease, with defective type 1 collagen formation. There are four main types with the main characteristic including bone fragility. OI is associated with dentinogenesis imperfecta which presents with widespread structural defects of the dentition and accelerated tooth wear (**Figure 42.6**).

Infections of the jaw bones

ALVEOLAR OSTEITIS (DRY SOCKET)

Alveolar osteitis is a localized osteitis which develops following a minority of dental extractions and is associated with breakdown of the tooth socket clot. Pain is severe, deep seated and localized to the socket and represents inflammation in the bone rather than infection. The cause is unclear but may represent ischaemia of the tissues as the condition is much more common in smokers. There also seems to be a familial tendency to develop a dry socket.

Clinical examination reveals an extraction socket with no clot with inflammation of the surrounding oral mucosa. Treatment is simply by local curetting of the bone walls of the socket allowing a blood clot to reform. Systemic antibiotics are not indicated.

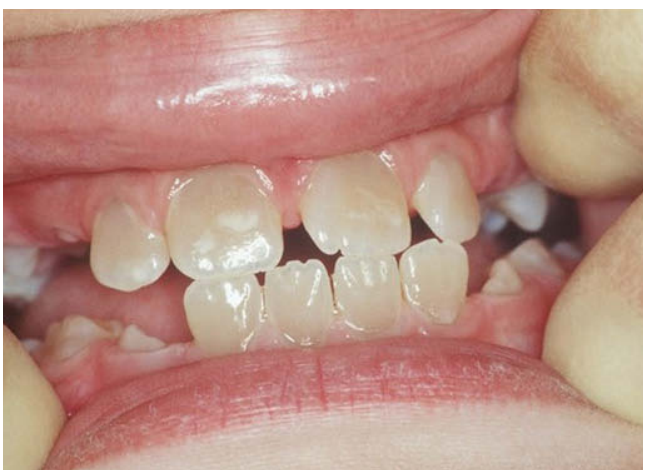

Figure 42.6 Dentinogenesis imperfecta.

OSTEONECROSIS

Osteonecrosis of the jaws may develop secondary to irradiation to the head and neck. In recent years there has been an increased incidence of medication related osteonecrosis of the jaw secondary to use of antiresorptive drugs such as but not exclusively, bisphosphonates and denosumab.

OSTEOMYELITIS

Both acute and chronic forms may occur in the jaw bones. Causes include spreading dental infection in the presence of a complicating factor such as immunosuppression. Osteomyelitis may also complicate an area of osteonecrosis. Treatment is through systemic antimicrobial therapy and surgical debridement.

Metabolic bone disease of the jaws

PAGET'S DISEASE OF BONE

The maxilla is the more frequently affected site and can be significantly increased in size thus creating occlusal disturbances and denture wear. Specific dental complications of Paget's disease include hypercementosis of teeth with the roots fusing with the alveolar bone resulting in ankylosis.

As in other sites, patients with Paget's disease of the jaws have an increased risk of malignant transformation to osteosarcoma.

Cysts of the jaw

Cystic jaw lesions may be classified using a variety of criteria such as developmental, or inflammatory, epithelial or non-epithelial, odontogenic or non-odontogenic. In adults, radicular cysts, which are inflammatory cysts, are the most common type, followed by developmental cysts such as dentigerous cysts (DCs).

The distribution and characteristics of jaw cysts in children are different from those in adults. In children, there is a relatively high rate of developmental cysts, whereas in adults inflammatory cysts are more common. Clinical presentation may vary depending on the type of cyst, size, site and structures affected. Cysts may also become infected with resultant signs and symptoms developing accordingly. It is important to appreciate that odontogenic tumours, both benign and malignant, may present as cystic lesions. Conversely, malignant change has been described to complicate both inflammatory and developmental cysts.

Odontogenic cysts, by definition, are formed from remnants of the tooth forming dental lamina and consequently involve the tooth-bearing regions of the jaws.

Inflammatory dental cysts

RADICULAR CYST

The radicular cyst is the most common inflammatory odontogenic cyst. This cyst arises around the apex or less commonly the lateral aspect of a non-vital tooth. Together with apical periodontitis, periapical granuloma, it is a

consequence of pulp infection and necrosis. The key to diagnosis is to demonstrate non-vitality of the associated tooth. If the tooth is vital a periapical radiolucency is not secondary to a periapical cyst.

If the culprit tooth is extracted, it is possible that cystic remnants of a periapical cyst will form a 'so-called' residual cyst. Treatment of the smaller periapical cyst is by extraction or root canal treatment of the involved tooth. When the periapical cyst is larger, treatment is as above, accompanied by surgical enucleation of the cyst.

Developmental cysts of the jaw

DENTIGEROUS CYST

The most common developmental odontogenic cyst is the dentigerous cyst (DC) and indeed is the most common cyst of the jaw in the paediatric age group. This cyst arises around the crown of an unerupted tooth with the wall of the cyst attached around the cervical margin of the involved tooth, with significant variation in size. DCs are more commonly unilocular but may also be a multilocular. Radiographically, a dental follicle-related radiolucency around an unerupted tooth should measure less than 4 mm from the surface of the tooth to the outer edge of the follicle; consequently any further increases should raise the possibility of cystic change. It is important to bear in mind that odontogenic tumours such as ameloblastoma and odontogenic keratocyst may involve unerupted teeth and present a diagnostic dilemma.

The treatment options include marsupialization or enucleation, with allogeneic or xenogeneic bone grafting. Harvesting of autogenous bone for grafting should be restricted to cases with large cysts and where bone substitute is not available. Enucleation of a cystic jaw lesion allows the entire surgical specimen and not only a biopsy specimen to be examined histopathologically.

Non-odontogenic developmental cysts

NASOPALATINE DUCT CYST

The embryological remnants of the nasopalatine duct may develop into a cyst. This may be an incidental X-ray finding with a radiolucency noted in this area or alternatively a swelling involving the nasopalatine papillary area is clinically evident coupled with the above-mentioned X-ray findings. The vitality of the adjacent teeth is intact.

Non-epithelial bone cysts

ANEURYSMAL BONE CYST

The aneurysmal bone cyst is controversially not considered a true cyst due to the absence of an epithelial lining. Presentation is most common in the mandible of children and young adults as a unilocular cyst. The size range varies with the potential to involve a significant proportion of the mandible. Radiographically, the radiolucency may have a scalloped appearance extending in between the roots of the teeth. Biopsy confirms the cyst cavity to be devoid of an epithelial lining. Healing may occur without treatment or consequence to an attempt at exploratory diagnostic surgery.

AMELOBLASTOMA

Ameloblastoma is an example of an odontogenic neoplasm that presents as a multicystic or unicystic lesion, locally infiltrative into bone marrow. Depending on the stage at diagnosis, the patient may be asymptomatic or at a later stage present with a swelling extensive jaw expansion. Both clinically and radiographically this tumour may need to be included in the differential diagnosis of a cystic lesion of the jaw. Histopathological confirmation is mandatory.

DISORDERS AFFECTING THE ORAL MUCOSA

Oral mucosal disease can be a reflection of anatomical changes or immunological processes within the oral cavity or an indication of systemic processes within the body. There are also a variety of irritants which produce visible changes in the mucosa on clinical examination.

Examining and recording changes of the oral mucosa

The oral mucosa should be examined using a good light source and suitable retractors, such as dental mirrors. The process should be systematic to ensure that all areas are considered and the recording of the findings presented in a reproducible and easily understood manner. The mucosa should be dried during the examination to allow proper visualization of any lesions. It is important to record negative as well as positive findings to avoid doubt in the future regarding changes in particular mucosal areas. Where appropriate, clinical photographs should be taken to record any lesions, particularly if monitoring is planned.

History taking for oral mucosal diseases

When taking a history from a patient with an oral mucosal disease, the clinician should ensure that the description of the presenting symptom is unambiguous. As an example, patients often refer to 'ulcers' in the mouth to mean any sore area. If the patient is using a word or phrase that has a specific meaning, the clinician must clarify the situation by direct questioning, such as 'Tell me what you mean by an 'ulcer''. Often, patients referred by their doctor or dentist may have no symptoms at all and a change in the expected appearance of the oral mucosa would have been noted by the practitioner as part of a routine oral examination.

Benign oral mucosal changes

A variety of oral mucosal changes may be noted on clinical examination that are either developmental, present as a result of normal oral function or are unexplained.

FRICTIONAL KERATOSIS

This is an adaption of the oral mucosa to increased trauma and results in a white thickening of the mucosal surface which often appears to be 'on top of' the existing mucosa. One common area where this can be seen is the area of the dental alveolus in a patient with missing teeth. This mucosa has increased trauma from food rubbing; an area previously protected by the teeth. The keratosis develops as a reactive change over time to reduce damage to the mucosal surface.

LEUKOEDEMA AND NICOTINIC STOMATITIS

This is a more generalized reactive white change to the oral mucosa, again in relation to generalized rather than focal irritation. Most commonly, this is a change seen in smokers where areas most in contact with the hot smoke are affected. This change can be much more prominent where there is a heavy smoke concentration, such as against the posterior hard palate, producing the changes seen in nicotinic stomatitis. In this condition, the dense hyperkeratosis with inflammation of the opening of the minor salivary gland ducts in the palate appear as red spots against the white background of the palatal mucosa.

FORDYCE SPOTS

The oral mucosa is not part of the developmental gut tube and is derived from the same elements that form the skin of the face. Various adaptations take place including the substitution of minor salivary glands for sebaceous glands. However, in some individuals the sebaceous glands still form in some areas and are visible through the mucosa as small yellow/white spots known as Fordyce spots. These are completely benign (**Figure 42.7**), most commonly seen on the buccal mucosa and the patient is normally unaware of them. They are also found on the lips in some individuals and women in particular, can find them a cosmetic problem.

TONGUE COATING

Many patients complain of having a 'coated tongue'. Occasionally this is a true overgrowth of the dorsal surface papillae and these can become stained to give the appearance of a 'brown hairy tongue' (**Figure 42.8**). More often, it is a slight exaggeration of the normal surface, as can happen when changing to a less abrasive diet or dehydration due to illness. A patient can become quite fixated about the appearance of their tongue, even in the absence of any symptoms.

The condition typically improves if the patient avoids habits or drugs that stain the tongue, such as dark beverages, smoking and chlorhexidine mouthwashes. The appearance can be improved by an increase in oral hygiene efforts and daily cleaning of the tongue dorsum by brushing the tongue with a toothbrush, use of sodium bicarbonate or peroxide mouthwashes, chewing gum or sucking a peach stone for 30–60 minutes each day.

GEOGRAPHIC TONGUE

Geographic tongue is a disorder of epithelial tissue turnover on the tongue dorsal surface. Very occasionally it can be found on other parts of the oral mucosa. Normal epithelial replacement occurs in scattered parts of the tongue mucosa at the same time and is not noticed, but in geographic tongue, adjacent epithelial areas have synchronized turnover with thinning of the mucosa as the existing layers are lost. This thinning makes the red colour of the connective tissue more visible and the patient describes red patches on the dorsum of the tongue which then gradually 'heal' as the new epithelium is produced (**Figure 42.9**). This entire process takes about 10 days but may be progressive over adjacent areas of the tongue which leads to the appearance of the condition 'moving' across the tongue. Although it can be a continuous process, it often occurs at intervals of 2 or 3 months in susceptible individuals. Most patients have no symptoms, but a proportion get sensitivity to highly flavoured or spicy foods due to the thinning of the epithelial barrier. This sensitivity is most noticed

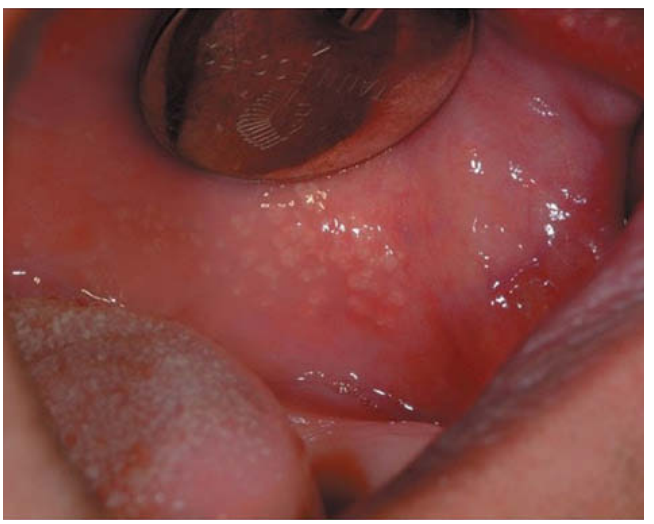

Figure 42.7 Fordyce spots.

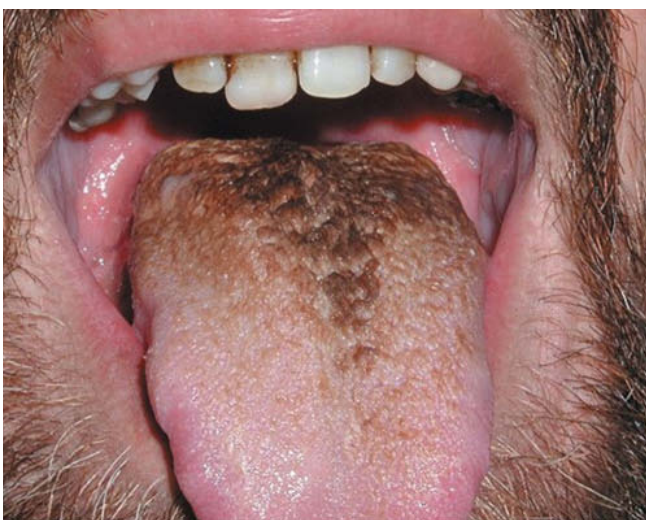

Figure 42.8 Brown hairy tongue.

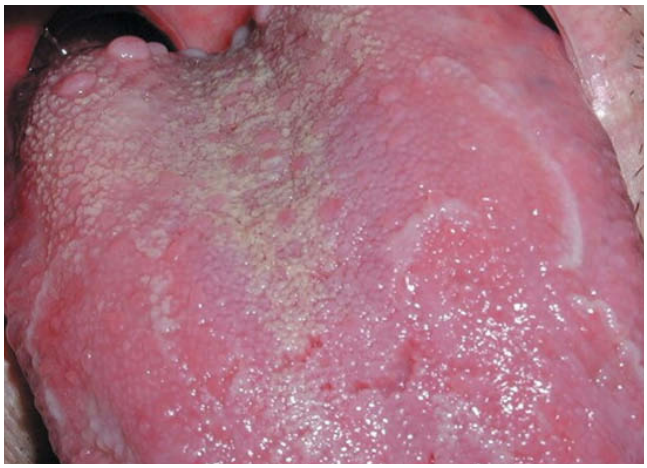

Figure 42.9 Geographical tongue.

by children and can be disabling particularly in the very young. With age, the sensitivity reduces and most symptomatic patients require no treatment other than avoiding irritant foodstuffs. Topical anaesthetics such as benzydamine can be helpful if symptoms are particularly bad, but as the cause for the reduced epithelial proliferation is unknown, no 'curative' treatments are available.

MEDIAN RHOMBOID GLOSSITIS

This is an uncommon condition that presents as a red, depapillated and smooth, rhomboidal area, broadly in the centre of the dorsum of tongue. It is usually associated with an invasive candidiasis which is not pathogenic. Multiple oral lesions may occasionally be present, especially a 'kissing' lesion in the palatal vault. Smoking, denture wearing and, occasionally, immune defects including HIV and diabetes are said to predispose to median rhomboid glossitis, but most lesions are seen in healthy adults. No treatment is required as the lesion is almost always asymptomatic, but a biopsy with PAS stain for candida can be useful for reassurance, particularly when the area becomes raised and lumpy.

MUCOSAL SWELLINGS

Thickening, hypertrophy and lumps of the mucosal structures can be reactive to a variety of local irritants or as a result of benign pathology of the oral or submucosal tissues. All of these lesions are typically painless.

Viral warts can produce thickening of the epithelium and are most commonly seen in children. When these present in an adult, immunosuppression is usually the cause and conditions such as HIV should be considered. Both extra- and intraoral warts usually arise as a result of contact with a skin lesion, such as on the hand or fingers, and all must be eradicated to prevent recurrence.

Fibro-epithelial polyps arise from low-level irritation and can be sessile or pedunculated. They only require removal if they are being subject to trauma, but the cause of the trauma should first be removed to prevent a continued increase in size or recurrence after removal. Multiple mucosal polyps, dental anomalies (hypodontia, enamel defects and taurodontism) and occasionally cleft lip and palate are found together in the rare Gorlin-Goltz syndrome and multiple mucosal papillomas with associated gastrointestinal (GI) and thyroid disease are found in Cowden syndrome.

Benign tumours in the connective tissue such as a neuroma, lipoma or minor salivary tumours such as the pleomorphic adenoma will produce small mobile lesions deep in the tissue. Mucoceles – obstructive minor salivary gland lesions – will usually have a history of waxing and waning on a recurrent basis, but may eventually fibrose to leave a firm connective tissue swelling.

Inflammatory swellings can arise on any part of the oral mucosa but are frequently seen on the gingival margin. The source of the irritation is often not obvious but a broken tooth may be a trigger. Pregnancy predisposes to gingival inflammatory swellings; most are pyogenic granulomas but giant cell lesions are also common. These latter lesions may be isolated localized lesions or part of a more widespread disease such as hyperparathyroidism. An X-ray should always be taken in the area of any gingival swelling to ensure that the soft-tissue lesion is not a bony lesion extending into the mouth.

Mucosal swellings can also arise as part of systemic disease including CD/orofacial granulomatosis, sarcoidosis, Wegener's granulomatosis and amyloidosis. Recurrent lip swelling is found in angio-oedema and orofacial granulomatosis.

Changes in mucosal colour

The oral mucosa is pink but as this is a view of the blood in the connective tissue beneath, the exact colour varies with the thickness of the epithelium and the vascularity of the underlying connective tissue. Consequently, the keratinized areas of mucosa such as the hard palate and gingival tissues appear whiter as there is a thicker barrier between the observing clinician and the connective tissue blood vessels.

White lesions of the oral mucosa are most commonly thickening of the epithelium by acanthosis or hyperkeratosis although reduced connective tissue blood flow can be seen in conditions such as submucous fibrosis (**Table 42.7**). An established squamous carcinoma will appear white as there is increased tissue in the area. White lesions are more

TABLE 42.7 White lesions of the oral mucosa

Local	Systemic
Frictional keratosis	Candidiasis
Smoker's keratosis	Lichen planus
Idiopathic keratosis	Lupus erythematosus
Carcinoma	Papillomas (some)
Burns	Syphilitic keratosis
Skin grafts	Inherited lesions (e.g. white-sponge naevus)

frequent, but are less commonly associated with dysplasia than red lesions. A white sponge naevus is a dominant-inherited developmental condition causing characteristic changes within the epithelium. It usually starts in childhood at the posterior buccal mucosa and spreads slowly anteriorly over years giving a characteristic appearance of a 'shaggy' white lesion covering much of the buccal and palatal mucosa including areas not subject to dental trauma such as the buccal sulcus. It is symptomless and requires no treatment.

Red changes of the mucosa usually reflect thinning of the mucosa making the observer more able to see the blood in the connective tissue but they can also arise as a consequence of increased vascularity of the connective tissue, as in the case of dysplasia or malignancy; thus, unexplained red lesions are of greater concern to the clinician. Inflammation of the tissues will also produce red changes to the mucosa, and commonly candida or other causes of mucosal irritation will give this appearance. Focal red lesions can represent capillary haemangiomas and require no treatment unless bleeding becomes an issue, usually secondary to trauma. Multiple focal haemangiomas are seen in the oral and facial tissues as part of hereditary haemorrhagic telangiectasia.

Pigmented lesions can be localized or generalized (see **Table 42.3**). Brown pigmentation is the result of increased melanin in the tissues. Biopsy can differentiate a melanosis (normal melanocyte numbers producing excess melanin) from a naevus (increased number of melanocytes each producing a normal amount of melanin). A melanoma is a rare primary lesion in the mouth.

Grey/blue pigmentation is seen with foreign bodies such as dental amalgam or heavy metal poisoning with lead or arsenic (**Figure 42.10**). These are best diagnosed on biopsy as the material is seen phagocytosed inside giant cells. X-rays are not reliable to demonstrate the small amount of foreign material and are discouraged as an investigation to reduce radiation exposure. Dark blue and purple lesions are mostly venous malformations such as a cavernous haemangioma or a varicosity and are seen in many elderly patients. If these lesions are raised enough to be subject to trauma and bleeding, they can be surgically excised or ablated with cryosurgery.

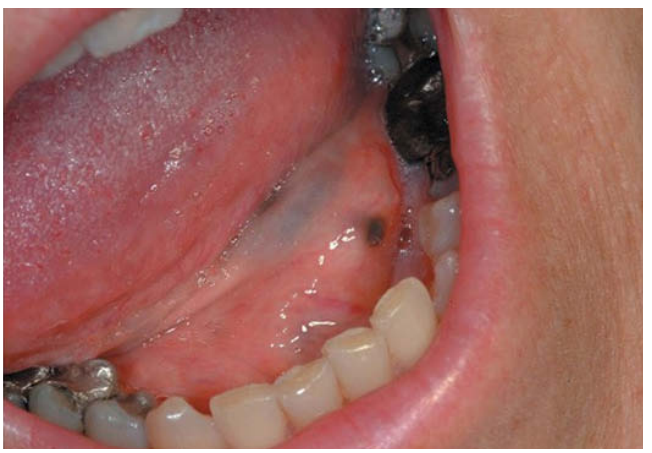

Figure 42.10 Amalgam tattoo.

Generalized oral mucosal pigmentation is most commonly racial pigmentation, whilst smoking is the commonest acquired cause. In smokers, the pigmentation fades when the habit is stopped. Medicines are another common reason for mucosal pigmentation with drugs as diverse as hydroxychloroquine, imatinib, minocycline and the oral contraceptive pill all implicated. Pregnancy or hormonal changes where ACTH levels are raised can also result in widespread oral pigmentation. Addison's and Cushing's diseases or some small-cell lung tumours are rare causes; for these reasons, an unexplained increase in pigmentation in the mouth should always be investigated.

Isolated or localized pigmentation can also be caused by any of the systemic causes for pigmentation; the observer may simply be seeing the start of the process. Localized lesions tend to have a local cause such as an amalgam tattoo where a tooth apicectomy has been performed, or post-inflammatory pigmentation in an area of trauma. However, the commonest cause is the simple melanotic macule or freckle but this should be confirmed on biopsy to differentiate it from a naevus or early dysplastic change. Peutz–Jeghers syndrome is an autosomal dominant trait characterized by hamartomatous intestinal polyposis and multiple areas of mucocutaneous melanotic perioral pigmentation.

Oral ulceration

Mouth ulcers are a frequent complaint by patients but the clinician must be clear as to what the patient means by 'ulcer'. This can be a term used to mean any sore spot in the mouth to a patient. A true ulcer is a break in the epithelium and may be preceded by a blistering phase in some conditions. It is important that this is clarified when taking the history. As oral ulceration can be a presentation of malignancy, any ulcer which has been present for more than 2 weeks must be investigated.

The common causes of ulcers include local trauma from teeth or sharp edges on dentures, recurrent aphthous stomatitis, Behçet's syndrome) and viral infections after the initial vesicle has burst. Systemic diseases associated with oral ulceration are given in **Table 42.8**.

The history should clearly differentiate a single continuing ulcer episode from recurrent oral ulcers and multiple oral ulcer lesions that overlap in time. Where an ulcer recurs in a specific area repeatedly a local cause should be considered, although ulcerated forms of lichen planus frequently present in this way.

APHTHOUS STOMATITIS

Aphthae are recurrent oral immunological ulcers that are multifactorial in origin and arise as a result of T-cell medicated damage to the mucosal epithelial basal layer (**Figure 42.11**). They are not potentially malignant lesions, occur throughout the GI tract and are characterized as major, minor or herpetiform depending on the presenting features (**Table 42.9**). All are genetically determined and this tendency may cause ulcers to be expressed spontaneously throughout life, or never at all depending upon the family characteristics. The family history is an important

TABLE 42.8 Oral ulceration associated with systemic disease

Causes	Examples
Microbial disease	Herpetic stomatitis Chickenpox Herpes zoster Hand, foot and mouth disease Herpangina Infectious mononucleosis HIV disease Tuberculosis Syphilis
Malignant neoplasms	Squamous cell carcinoma Lymphoma
Skin disease	Erosive lichen planus Pemphigus Pemphigoid Erythema multiforme Dermatitis herpetiformis and linear IgA disease Epidermolysis bullosa
Systemic triggers for ulcers Blood disorders	Rapid growth periods during childhood Haematinic deficiency (ferritin, folate, vitamin B_{12}) Leukaemia Neutropenia Other white cell dyscrasias
Gastrointestinal disease	Coeliac disease Crohn's disease Ulcerative colitis
Iatrogenic causes	Antirheumatic drug therapy Chemotherapeutic agents Acrodynia Radiotherapy

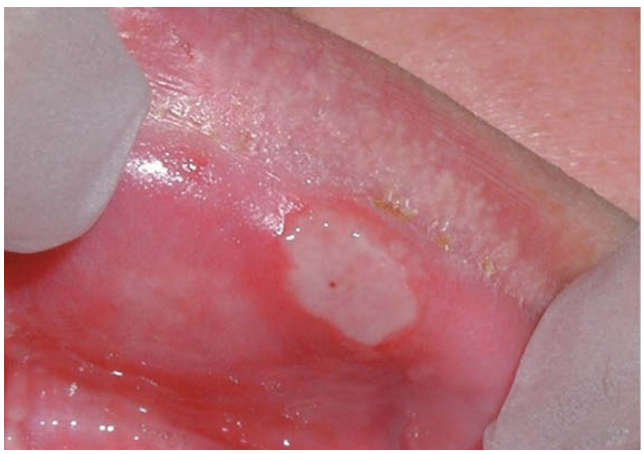

Figure 42.11 Aphthous ulcer.

predictor of the ulcer pattern in an individual. In addition to the genetic susceptibility are a range of health and environmental modifying factors which can promote ulcer formation; the combination of genetic and environmental triggers determine the individual's susceptibility to aphthae. If an individual has had recurrent aphthous oral ulcers since childhood then the genetic component is likely to be the main ulcer determinant, but if there has only been the occasional ulcer until recently it is more likely that a modifiable environmental or health factor could be at play, leaving the opportunity for successful medical intervention. The most common correctable triggers are haematinic deficiencies, where iron (measured as ferritin), folic acid or vitamin B_{12} levels are low. This can happen in the presence of a normal blood count and the absence of anaemia does not exclude a haematinic deficiency. A haematinic screen together with a coeliac screen should be carried out for all patients with recurrent aphthous stomatitis.

TABLE 42.9 Aphthous ulceration

Type of aphthous ulceration	Clinical features
Minor aphthous ulceration	Most common form of aphthous ulceration Less than 10 mm in diameter Last 2–3 weeks Only on non-keratinized mucosa Heal without scarring Can be multiple but fewer than 10 at a time Usually at the front of the mouth Commonly in areas of mucosal trauma
Major aphthous ulceration	Larger than 10 mm in diameter Can last up to 3 months Can occur on keratinized or non-keratinized mucosa Can heal with or without scarring Usually single but 1–3 ulcers can be present at once Usually towards the back of the mouth
Herpetiform ulceration	Least common form of aphthous ulceration Less than 5 mm in diameter Last for up to 2 weeks Heal without scarring Large numbers of ulcers – up to 100 Coalesce in areas to form large areas of ulceration Arise in keratinized and non-keratinized mucosa Similar in appearance to primary herpetic gingivostomatits

As aphthous ulcers are driven by an immunological reaction, the process can be controlled using immunomodulatory therapy. In some cases, altering environmental factors such as avoiding sodium lauryl sulphate (SLS) containing toothpastes or dietary triggers (benzoate, chocolate, cinnamon) can reduce the triggering of lesions to a level low enough to satisfy the patient. In others, the use of topical immunosuppressants or immunomodulators can successfully alter the clinical course of the disease. As the immunological damage happens some days before the ulcer appears, it is critical that the treatment is started as soon as the patient becomes aware of the lesion. By the time the ulcer appears, it is too late for an immunomodulatory drug to be effective and the patient must rely on analgesic solutions or obturative pastes to manage their symptoms. Treatment options for aphthous ulcers are listed in **Table 42.10**. Systemic immunotherapy should only be used by a specialist with appropriate experience.

Erythema multiforme (EM) is an immunological hypersensitivity reaction that can affect many body systems

TABLE 42.10 Treatment options for aphthous ulceration

Treatment modality	Medication	Instructions
Symptomatic	Benzydamine solution	Spray solution onto ulcer or rinse with the solution for one minute before meals to reduce ulcer sensitivity
	Occlusive paste (e.g. orabase) Lignocaine gel	Apply to the ulcer before eating to give relief from discomfort
Topical episodic	Betamethasone mouthwash	1 mg dissolved in 10 ml water, use as rinse for 2 mins twice daily at the onset of ulcer symptoms until ulcer heals
	Beclomethasone Inhaler 50–200 mcg/puff	Give 2 puffs of the powder three times daily directly onto the area with ulcer symptoms starting at the onset of symptoms until the ulcer heals
Topical preventative (*can be combined into a single mouthrinse*)	Betamethasone mouthwash	1 mg dissolved in 10 ml water, use as rinse for 2 mins once daily each day
	Doxycycline mouthwash	100 mg soluble tablet in 10 ml water used as a rinse for 2 mins twice daily
Systemic preventative	Colchicine Azathioprine Mycophenolate mofetil	Used under the direction of a specialist only

individually or together (Stevens-Johnson syndrome). There may be a genetic predisposition to recurrent erythema multiforme and this is seen most commonly in young men. In the mouth, EM presents in much the same way as a primary herpetic gingivostomatitis with widespread oral mucosal inflammation and multiple areas of coalescing ulceration on both keratinized and non-keratinized mucosa. This may be the only clinical lesion, but in other patients the oral lesions may appear concurrently with skin, genital or nasopharyngeal lesions. EM appears to be a type 3 hypersensitivity reaction where a host antibody binds an antigen in the circulation and lodges in capillary tissue, activating complement and initiating localized inflammation and tissue damage. The labial mucosa is often involved, and a serosanguinous exudate leads to crusting of the swollen lips.

The following are possible triggers for EM: infective agents, particularly HSV and mycoplasma; drugs such as sulphonamides, cephalosporins, aminopenicillins, quinolones, NSAID; food additives or chemicals such as benzoates, nitrobenzene, perfumes, terpenes.

The diagnosis can be difficult and a biopsy of perilesional tissue, with histological and immunostaining examination are essential if a specific diagnosis is required. Supportive care is important; a liquid diet and intravenous fluid therapy may be necessary. EM should be treated with high-dose systemic corticosteroids in the acute phase. Preventative therapy with acyclovir can be helpful if recurrent lesions are suspected to be from a HSV reaction.

Mucositis (mucosal barrier injury) is the widespread erythema, ulceration and soreness which commonly complicates chemo-, radio- or chemoradiotherapy. Mucositis appears from 3 to 15 days after treatment, earlier after chemotherapy and radiotherapy. Mucositis invariably follows total body irradiation and external beam radiotherapy involving the orofacial tissues. Up to 90% of patients on traditional chemotherapy develop mucositis although targeted cancer immunotherapy is less likely to give ulcers. Oral mucositis is particularly severe after haemopoietic stem cell transplant and can act as a portal for infection. Mucositis typically presents with pain which can be intense enough to interfere with eating, and significantly affect quality of life, with ulceration and sometimes bleeding.

Management aims to relieve pain, hasten healing and prevent infectious complications. Pain relief is usually with opioids given by patient-controlled analgesia; additionally, benzydamine rinse or spray can aid relief. Oral cooling with ice chips ameliorates chemotherapy-induced mucositis.

Systemic diseases and the mouth

The oral mucosa is a specialized form of skin bridging the gap between the embryonic gut tube ending and the outside world as the head and brain rapidly enlarge. The mouth therefore has a stratified squamous epithelium lining and the transition to the gut 'proper' happens in the oesophagus. Consequently, the oral cavity experiences a transition of diseases between GI and dermatological conditions and skin appendages can result in visible changes in the mouth in some individuals.

DISEASES OF THE SKIN

The immunobullous conditions pemphigus, pemphigoid and lichen planus are commonly present with findings in the oral mucosa. Others seen more rarely include epidermolysis bullosa and linear IgA disease.

Pemphigus and pemphigoid are autoimmune disorders driven by immunoglobulins, where C3 and IgG binding cause loss of adherence of intercellular desmosomes and hemidesmosomes. They result in separation of the cells of the epithelium from each other (pemphigus) and the epithelium from the basement membrane (pemphigoid). Pemphigoid presents with a combination of intact and ruptured bullae but pemphigus has such fragile intraepithelial bullae that they are frequently not seen other than as a white change in the mucosa which is rapidly lost to reveal a red and inflamed submucosa (**Figure 42.12**). There are variations in these diseases depending upon the epitopes of the antigen

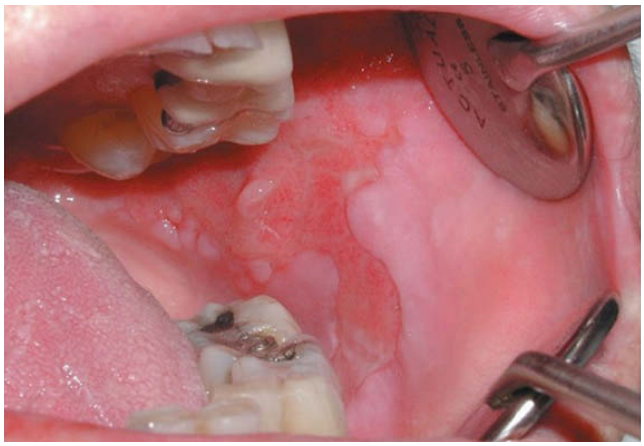

Figure 42.12 Pemphigus.

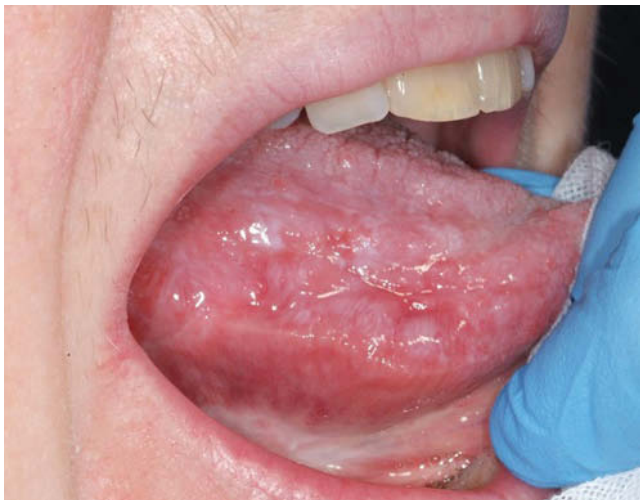

Figure 42.13 Lichen planus.

targeted by the immune reaction and these small alterations can significantly change the presentation or consequences of the disease processes. There are also differences between the immune target in the skin and oral versions of these conditions such that they can run largely independent courses in the same individual. Pemphigus often will start with oral lesions and later involve the skin whereas pemphigoid can have limited oral and cutaneous versions. Pemphigoid also has a scarring form limited to the mucosa and into the eyes and oesophagus – cicatricial pemphigoid. This is progressive and can be very disabling over time with difficulty opening the mouth and swallowing as well as significant ophthalmological issues.

All patients diagnosed with pemphigoid on the oral mucosa should see an ophthalmologist to manage any conjunctival scarring which may appear with time. Most symptoms from these conditions result from the ulcerative areas left when the bullae burst (pemphigoid) or the epithelium separates internally (pemphigus). This causes widespread discomfort for the patient.

Paraneoplastic pemphigus is suspected when a pemphigus lesion is difficult to manage. It is usually associated with lymphoproliferative disease or thymoma and the oral lesions may be the sole manifestation. A degree of suspicion is needed but an appropriate referral to a general physician for assessment is essential. Biopsies for pemphigoid and pemphigus must be taken from perilesional tissue otherwise no epithelium will be present on the specimen for proper examination.

Lichen planus (LP) is a very common oral condition and in most patients, is asymptomatic. It is a T-cell mediated attack on the basement membrane and basal cell layer of the skin or mucosa and causes a reactive increase in the epithelial width (acanthosis – white appearance) or a reduction in the production of new epithelial cells and a consequent reduction in epithelial width (atrophy/ulceration – red appearance). Both can be present in the same lesion at the same time. On the skin it gives lacy patterns, with itchy purple spots on the wrists, legs and trunk. About 30% of patients have both oral and cutaneous lesions. The oral lesions are frequently asymptomatic and seen as an incidental finding on oral examination. However, oral LP can present in more aggressive ways including atrophic and erosive versions which cause discomfort with spicy and flavoured foods. Lesions tend to be intermittent and recurrent and can be symptomatically confused with recurrent aphthous ulcers. However, LP lesions tend to recur in the same places repeatedly whereas aphthae vary in position. Common sites for LP are the lateral aspects of the tongue and the buccal mucosa (**Figure 42.13**). LP has a low potential for malignant transformation although the individual risks for a lichenoid lesion are not clear. Patients must be made aware of the issue of possible malignancy so that regular monitoring of the lesions can take place. LP is mostly of unknown origin but in some individuals, there is a trigger from amalgam or other dental restorations adjacent to the lesions. This is termed a lichenoid reaction although the lesions on the mucosa are essentially the same as those seen in LP. Drug reactions can also trigger a lichenoid reaction, the commonest of which are ACE inhibitors and beta-adrenergic blockers. Disease-modifying drugs used in connective tissue diseases such as gold, penicillamine and sulphasalazine are used less frequently now but were frequent triggers in the past. Discontinuing these medicines gradually results in an improvement in the condition. Angiotensin-2 receptor blockers do not give this reaction and are a good alternative where an ACE inhibitor is suspected as the cause of the lichenoid reaction.

All three of these dermatoses can also present in limited form in the mouth, affecting the attached gingivae only. This is clinically described as a 'desquamative gingivitis' and the underling condition can be determined by biopsy (**Figure 42.14**).

Management of pemphigus, pemphigoid and LP uses the same algorithmic approach as is used for aphthous ulcers (**Table 42.10**) with the exception of colchicine which has no role in the immunobullous conditions. Additionally, topical clobetasol or tacrolimus as a cream or ointment can be useful for stubborn but localized lichenoid lesions. Tacrolimus as a mouth rinse can be a useful bridge between topical steroids and systemic medication for

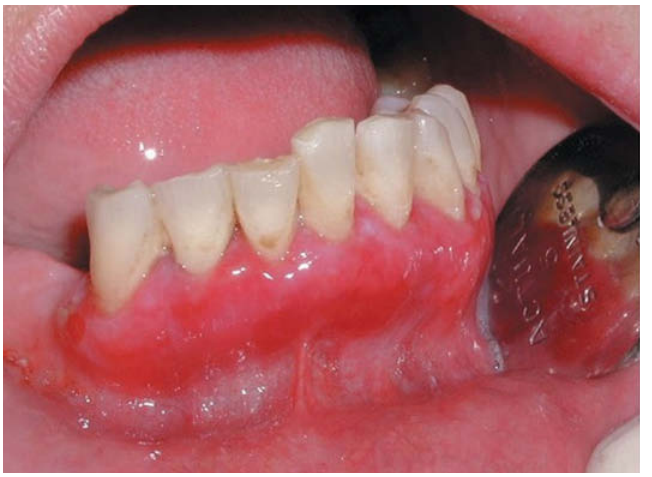

Figure 42.14 Desquamative gingivitis.

individuals with widespread lichenoid lesions but is ineffective against pemphigus and pemphigoid in the mouth as they are largely antibody rather than T-cell driven.

Diagnosis of an immunobullous condition in the mouth is by perilesional biopsy with one sample sent for standard histopathology and a second sample for direct immunofluorescence. Indirect immunofluorescence from a blood sample is not accurate as a diagnostic test but can be helpful in monitoring disease activity.

GASTROINTESTINAL DISORDERS

GI conditions are frequently associated with oral symptoms and signs. The consequences for the oral mucosa can be direct disease effects or secondary to nutritional deficiency from GI bleeding or malabsorption. Oral ulcers, candida infections and lichenoid lesions are all exacerbated by haematinic deficiency and thus, blood loss from peptic ulcer disease, inflammatory bowel disease or bowel cancer will impact on the mouth, and may be the presenting symptom.

Coeliac disease is often easy to diagnose in children as there is growth failure. However, adult-onset coeliac is more of a challenge and the nutritional deficiency consequent to malabsorption may exacerbate oral diseases. Commonly ferritin and folic acid levels are reduced when there is small bowel malabsorption and this combination should always raise suspicion. Where necessary a tissue transglutaminase or more specific coeliac test can be run.

Ulcerative colitis (UC) similarly can exacerbate oral conditions that are sensitive to haematinic deficiencies. However, aphthous pattern mouth ulcers can occur during periods of UC activity and the oral lesions tend to settle when the colonic disease is controlled.

Crohn's Disease (CD) is a pan-GI disorder with full-thickness inflammation of the mucosa, lymphatic obstruction and mucosal oedema. Like UC its aetiology is unknown but likely represents a range of aetiologies interacting with the host immune system. First symptoms can commence at any age and localize to any area of the GI tract; akin to UC, exacerbation of oral conditions related to haematinic deficiencies complicates the condition. CD can involve the mouth together with other GI sites and when there is gut disease present the oral features are described as 'oral Crohn's disease'. In children, the oral features may present before GI symptoms.

Oro-facial Granulomatosis (OFG) is a disease which has all the features of CD but is localized to the oral mucosa with no symptomatic GI disease. Over time some will develop GI symptoms and OFG may represent part of the spectrum of CD rather than being a separate entity. As sarcoidosis and tuberculosis can both present in the mouth with similar clinical findings, it is important that these are excluded before a diagnosis of OFG is attributed. The characteristic features of OFG are identified in **Box 42.1**.

Not all of these findings are present in every patient and recurrent or persistent lip swelling usually triggers the referral. These lip swellings are from lymphoedema with the lymphatics obstructed by giant cells. The swelling persists for several days or weeks at a time. Like CD it is likely that the aetiology of the immunological reaction in OFG is multifactorial and varies from patient to patient.

Management of OFG takes two approaches. First, the lymphoedema can be reduced in patients who have a sensitivity to dietary triggers by a 12-week complete exclusion diet. It is not possible to identify these patients other than by the diet and so all OFG patients are started with this regime. The patient needs to exclude benzoate, sorbate, cinnamon and chocolate. This requires a degree of determination by the patient and others in the household if it is to be a success. Advice from a specialist dietician can be helpful. During the exclusion period those patients with dietary hypersensitivity will get progressive reduction of the lip swelling although some of the other intraoral changes will persist. At the end of the exclusion period, the patient can return to a normal diet if exclusion was ineffective or, if it was helpful, individual foodstuffs can be reintroduced one at a time to identify individual items for future avoidance. It is unclear whether these dietary triggers are implicated in the aetiology of OFG or are coincidental issues present in the patient for many years and brought to the fore by the lymphatic obstruction.

The second management approach is to use immunotherapy to eliminate the giant cell reaction and allow the lymphatics to drain freely. This can be tried with topical tacrolimus but usually needs systemic treatment with azathioprine of mycophenolate. Surgical options for OFG management usually produce a poor cosmetic result.

BOX 42.1 Oral features in Crohn's disease

- Lip and/or facial swelling and erythema
- Angular cheilitis
- Oral mucosal tagging
- 'Cobblestone' appearance of the mucosa
- Linear ulcers in the depth of the buccal sulcus
- Non-plaque related full width gingival inflammation

CONNECTIVE TISSUE DISORDERS

Most connective tissue disease affecting the head and neck involves the salivary glands. However, mucosal lesions from lupus erythematosus or loss of tissue elasticity as a result of scleroderma can complicate oral care.

Discoid lupus lesions or those associated with SLE have a clinical appearance like lichen planus but are distinct on biopsy. The lesions are also more commonly found in sites unusual for lichen planus, such as the mucosa of the palate.

Scleroderma either on its own or as part of CREST syndrome poses many challenges for oral care. Once the disease fully takes hold, mouth opening is greatly reduced and dental care including denture provision becomes extremely difficult. When it is clear a patient has oral involvement from scleroderma, an opinion should be obtained from a Restorative Dentistry specialist who can assess the long-term prognosis for the dentition and plan for a future low-maintenance mouth.

GRAFT VERSUS HOST DISEASE

Graft versus host disease (GVHD) is usually the consequence of allogeneic bone marrow transplant but is also seen after autologous stem cell treatment. The oral lesions are similar to a widespread lichenoid reaction and mirror the immunological damage taking place elsewhere in the body. The oral lesions can be painful if erosive or atrophic and can be managed with topical steroids in most cases. However, the patient's physician should be made aware of the oral finding as systemic immunotherapy may be preferred to prevent concurrent damage to other body organs. Herpes simplex virus (HSV) causes primary herpetic stomatitis of the oral and genital areas with oral lesions accompanied by systemic upset and fever. Either HSV1 or 2 can be found in primary or recurrent lesions. Many infections with HSV occur in childhood and are subclinical, often misdiagnosed or passed off as 'teething'. More typically it presents with malaise, anorexia, irritability and fever, anterior cervical lymphadenopathy and a diffuse, purple, boggy gingivitis with multiple vesicles followed by scattered ulcers 1–3 mm in diameter. A full blood picture, white cell count and differential, and viral studies may therefore be required. Specific antiviral agents such as aciclovir are reserved for immunocompromised patients. Recurrent HSV lesions can be seen periorally but can also present as intraoral lesions, most typically on the palate. The patient describes a recurrent 'ulcer' in an area which is unilateral and restricted to a single mucosal nerve branch. Where symptomatic, the intraoral and extraoral lesions can be treated symptomatically. In significant lesions which are disfiguring or persisting, systemic acyclovir is used in preference to topical drug. A continuous low dose of aciclovir can be given each day as prophylaxis against recurrence and can significantly improve the patient's quality of life.

Herpes Zoster virus (HZV) causes similar clinical lesions as found in HSV but the primary infection (chicken pox) has skin lesions as well as the oral vesicles/ulcers and systemic fever. The HZV virus is more neuropathic than HSV and the characteristic difference when recurrent lesions (shingles) appear in the mouth or on the face is pain in the affected area, which may precede the onset of the vesicular rash. Shingles should always be treated with aciclovir to reduce the cumulative nerve damage that can lead to post-herpetic neuralgia. The medication should be started with the onset of pain and continued until the rash has cleared. The dose of aciclovir needed to treat HZV is higher than with HSV and similarly, if daily prophylaxis against recurrent HZV is to be given, the dose must be raised above that used for HSV.

Other herpes group viruses also cause oral mucosal lesions. Epstein–Barr virus (EBV) gives the features of glandular fever during the primary infection and although there is no mucosal recurrent lesion as with HSV, persistence of the virus can be associated with hairy leukoplakia in the immunocompromised and nasopharyngeal carcinoma. Cytomegalovirus (CMV) rarely causes oral issues except in the extremely immunosuppressed patient where widespread atypical oral ulceration can arise, a difficult clinical problem. *HHV8* is associated with Kaposi's Sarcoma oral lesions.

Human papillomavirus (HPV) is present in mucosal warts and multiple wart-like lesions in an adult should raise the suspicion of immunodeficiency. HPV seems not to be associated with oral squamous cell carcinoma although it plays a significant role in oropharyngeal cancer.

Coxsackie viruses can cause hand, foot and mouth disease, and herpangina with oral vesiculation together with systemic symptoms but treatment for the oral lesions is supportive only.

HIV-associated oral lesions have been well documented but with the advent of HAART management these are now rarely seen except in the latter terminal stages of the disease. Consequently, an HIV test should be considered in any patient presenting with an oral condition noted to be associated with immunosuppression (**Figure 42.15**).

FUNGAL INFECTIONS

Candida albicans is the most common fungal organism found in the mouth although other forms such as *C. krusei, C. glabrata C. tropicalis* and *C. dubliniensis* can be

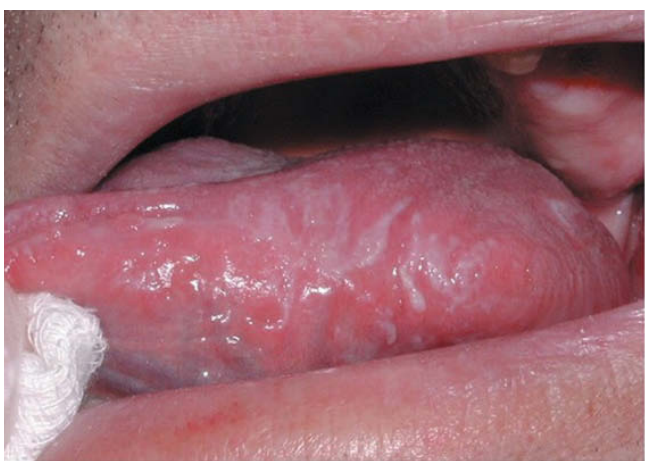

Figure 42.15 Hairy leukoplakia in HIV.

TABLE 42.11 Rare orofacial fungal infections

Infection	Oral manifestations
Aspergillosis	Aspergilloma Rhinocerebral type causes palatal necrosis Disseminated in immunocompromised patients
Blastomycosis	
North American South American (paracoccidioidomycosis) Coccidioidomycosis Cryptococcosis Histoplasmosis Phycomycosis (mucormycosis, zygomycosis)	Oral ulcers, or suppurating granulomas
	Oral ulcers and lymphadenopathy
	Rarely oral ulcers
	Oral ulcers
	Lumps or ulcers
	Antral involvement with palatal ulceration in immunocompromised patients – especially diabetics

TABLE 42.12 Oral *Candida* conditions

Types of candidiasis	Predisposing factors
Acute pseudomembranous candidiasis (thrush)	Local or systemic immunosuppression
Acute atrophic candidiasis (antibiotic sore mouth)	Broad-spectrum antibiotics
Erythematous candidiasis	None, aging
Chronic atrophic candidiasis (denture-related candidiasis)	Denture/appliance-wearing, especially at night
Chronic hyperplastic candidiasis	Tobacco smoking
Median rhomboid glossitis	Tobacco smoking, denture wearing, local immunosuppression
Angular cheilitis	Denture wearing, diabetes, haematinic deficiency, OFG
Chronic mucocutaneous candidiasis	Often immune defect; rarely endocrinopathy

found. These non-albicans species tend to be more resistant to common antifungal agents. Rarer orofacial fungal infections are listed in **Table 42.11**.

Candida spp. is a commensal in many of the population and a swab from the mouth demonstrating *candida* does not denote infection, simply candidial carriage. Quantitative fungal assays can be used where it is important to demonstrate high levels in the mouth. *Candida* can cause a variety of oral infections and appearances (**Table 42.12**). Although acute pseudomembranous candidiasis can produce white lesions in the mouth the clinician will do well to remember that there are many causes of oral white lesions and that every patient with a white lesion should not be assumed to have, and be treated for, candidiasis!

Denture-related stomatitis (chronic atrophic candidiasis) is the most common form of mild, chronic, oral candidiasis. It occurs only beneath a denture or other appliance and, despite its name, is not often sore. Dentures worn throughout the night, or with a dry mouth, favour development of this infection and occasionally there is a mixed infection with staphylococcal species. An accumulation of microbial plaque on and in the fitting surface of the denture and the underlying mucosa predispose to making the clinical appearance persist. This condition is managed exclusively by proper denture hygiene including removing the denture at night, cleaning the denture properly and treating it regularly with an appropriate antiseptic. There is no need for a topical antifungal except in the immunocompromised. If untreated the patient may develop papillary hyperplasia of the tissues beneath the denture which can complicate the provision of a new denture in the future.

Acute oral candidiasis (acute pseudomembranous candidiasis) may complicate systemic, topical or inhaled corticosteroid or antibiotic therapy (**Figure 42.16**). It produces widespread erythema and soreness or the mouth and pharynx, sometimes with thrush.

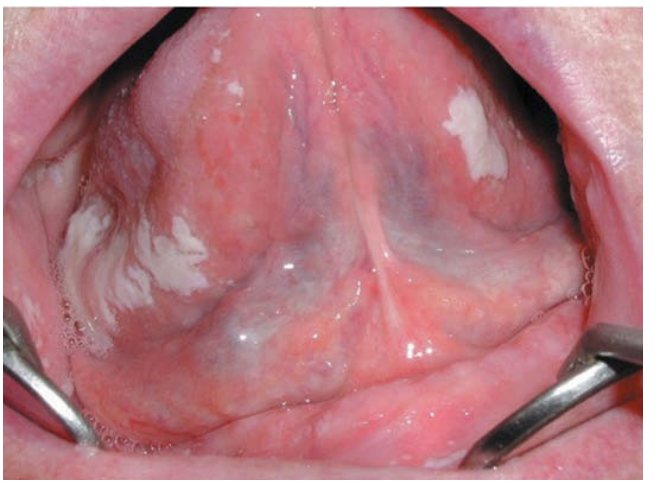

Figure 42.16 Pseudomembranous candidiasis: 'thrush'.

In some immunocompetent patients, there is persisting erythema in the palatal tissues associated with candida. This is termed chronic erythematous candidiasis and requires no treatment.

Chronic hyperplastic candidiasis (CHC) is a condition that has been considered potentially malignant but the link between CHC and oral cancer is now less clear. Its true nature remains elusive but it is associated with candida invasion into the tissues at the corners of the mouth causing a raised white lesion on the oral mucosa. Histologically, the picture is often that of high-grade dysplasia, but this is a reactive change to the presence of candidial hyphae in the tissues. When systemic antifungals are given, the dysplastic appearance settles and it is essential that where dysplasia is reported in CHC, the patient is given a systemic antifungal and the tissue re-biopsied to ensure that the tissue changes resolve. The fungal invasion and the clinical picture will usually return in time and may need repeated systemic antifungal courses.

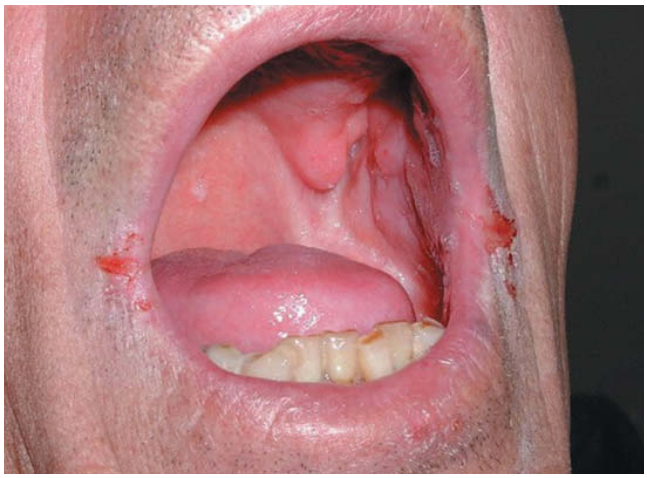

Figure 42.17 Angular stomatitis.

Angular stomatitis is a fairly common acute or chronic inflammation of the skin and contiguous labial mucous membrane at the angles of the mouth, bilaterally (**Figure 42.17**). Most cases are in adults and due to mechanical and/or infective causes but, in children, nutritional or immune defects are more prominent causes.

Mechanical factors include dentures with an incorrect facial height, no denture worn in edentulous patients or as a normal consequence of the ageing process in some patients. This can result in overfolding of the mouth corners and leakage of saliva. This is a strong irritant to the skin at the corners of the mouth. Nutritional deficiencies, in particular iron, folate and vitamin B_{12} make this change more likely. It is also seen to be associated with orofacial granulomatosis, diabetes and HIV infection. *Candida spp.* or staphylococci are isolated from most patients and topical miconazole treats both of these organisms. There is a benefit from using a preparation with miconazole and hydrocortisone as it allows for quicker reduction in the inflammation of the skin and the re-establishment of a proper infective barrier. This reduces recurrence of the condition.

Orofacial pain

Most oral pain is from common dental and periodontal inflammatory causes such as pulpitis, periapical periodontitis and pericoronitis. Neurological, vascular and referred causes are less common. Non-dental and idiopathic facial pain are common in specialist settings and present to dentists, general practitioners, neurologists and oral surgeons as well as oral medicine and ENT specialists. Often a patient has multiple referrals to a variety of specialist services from different practitioners and these other specialty contacts must be identified in the history so that collaborative working can take place.

Chronic oral mucosal soreness can arise from persisting ulceration or mucosal atrophy secondary to lichen planus, major aphthous ulceration, geographical tongue and haematinic deficiency states. Other distinct groups of orofacial pain conditions cluster around trigeminal autonomic cephalgias, oral dysaesthesias and temporomandibular disorder.

Glossitis is not a true condition but the term is frequently used. Tongue pain may be related to deficiency of iron, folate or vitamin B_{12}, and may present in association with other deficiency-related oral issues such as angular stomatitis and/or aphthous ulcers. A full blood count and assays of iron (ferritin), folate and vitamin B_{12} are indicated. The clinical appearance of the tongue may show generalized or localized depapillation predominantly of the filiform papillae. The tongue may appear fissured and erythematous but this is a normal variation and not the source of any discomfort reported by the patient. Lichenoid atrophy of the tongue dorsum and candidial invasion of the tongue surface can also give tongue sensitivity and pain and a biopsy is indicated if there is doubt about the cause of the patient's symptoms.

TRIGEMINAL AUTONOMIC CEPHALGIA

The extremes of this group of facial pain and headache conditions are recognized as trigeminal neuralgia and cluster headache. However, it is now clear that this is a spectrum of disorders with any one individual having features closer to either condition or a blend of both. Importantly, patients can move along the spectrum with time changing the presenting symptoms and the treatment needed to remain pain free.

Trigeminal neuralgia (TN) is a condition of unknown origin which causes a characteristic pain on stimulation of a particular sensory nerve area. This is usually on the surface of the face or in the mouth but can be deeper in the tissues and even the teeth and is usually worse over the winter months. If the same condition affects the mucosa of the posterior tongue or pharynx it is labelled glossopharyngeal neuralgia and this has implications for the management options. TN is mostly seen in patients over 50 years of age but there are an increasing number of younger patients presenting. In the classical form TN presents with a trigger area which, when touched, causes a severe but short-lasting pain radiating from the trigger area through the trigeminal distribution. In most cases, this is the maxillary or mandibular divisions of the trigeminal nerve. Usually a single unilateral area is affected. In some cases, the pain may be followed by a burning sensation in the trigger area. Hypoaesthesia in the trigger area should raise suspicion of an intracranial mass lesion such as an acoustic neuroma or a degenerative brain disease, both of which can present with TN. Rarely TN can follow maxillofacial trauma with the trigger in the area of the injury, such as a previous zygomatic or mandibular fracture.

MRI is an essential first investigation when TN is suspected and medical therapy should be instituted quickly. The medication of choice is determined by the patient's other medication, medical and home circumstance and the treating physician's experience with TN patients. Carbamazepine is often the first-line medication but it causes significant sedation, balance disorders, nystagmus and drug interactions. Oxcarbazepine and lamotrigine are effective alternatives with fewer side effects in most patients. Lamotrigine must be introduced over several weeks and is often used once initial symptom control is achieved with carbamazepine.

Surgical treatment for TN is indicated in the young or where the dose of medication is significantly impacting on the patient's quality of life. A microvascular decompression is the treatment of choice where the MRI indicates that a vascular loop is compressing the trigeminal root. This procedure will usually result in a pain-free patient, off medication for several months although lower doses of the anti-neuralgic medicines are needed eventually. Destructive procedures to the trigeminal ganglion are quicker and simpler operations for the less fit patient and stereotactic radiosurgery (gamma knife) requires no operation at all.

Cluster headache (CH) is a condition of unknown origin which has unilateral pain and autonomic efferent features including ptosis, facial erythema/swelling, lacrimation and nasal discharge on the affected side. It has both episodic and chronic forms. The former will give several weeks of daily intense headache and facial pain before terminating abruptly whereas the latter gives daily pain with no respite. In CH the pain lasts several hours, is unbearable for the patient and stops spontaneously after 3–5 hours. It often happens at night or in the evening and there is an association with coffee use. Management is for specialist practice. Inhaled oxygen with the onset of pain can be very effective but triptans have a place in some cases. Chronic CH has been reduced in severity and frequency using verapamil at moderate to high doses; lithium has also been used as a preventative therapy.

ATYPICAL ODONTALGIA

Patients with this condition often have a strange pattern of dental extractions on looking in the mouth. Most often there is a single mouth quadrant where many teeth have been removed in an otherwise healthy mouth. This condition is characterized by intense toothache focused on a single tooth. This usually has no evident disease but the patient is in such intense pain the tooth is eventually root treated and finally extracted. The pain settles but in a few weeks or months returns in the same quadrant of the mouth in an adjacent tooth. The pattern repeats. If, eventually, all of the teeth are removed the pain settles in the edentulous bone with the same characteristic toothache. This appears to be a neuropathic pain problem but even with current medication if can be challenging to treat.

PERSISTENT IDIOPATHIC FACIAL PAIN

This is a diagnosis of exclusion and consequently can reflect the clinician's diagnostic ability as much as the pain problem itself. It is best made by a specialist in oro-facial pain who can exclude some of the rarer but treatable head and neck pain problems. The older term of atypical facial pain should not be used.

ORAL DYSAESTHESIA

Oral dysaesthesias are a group of conditions in which the patient seems to have altered perception of the oral environment such that the mouth feels dry, burning, numb or with a bad taste/smell in the absence of any disease. They are often referred to as burning mouth syndrome although the most common presenting variation is that of a feeling of oral dryness or stickiness in the presence of plentiful oral saliva. These conditions represent a misperception of the normal oral environment rather than a disease of the oral mucosa or supporting tissues. Patients will often have more than one dysaesthesia symptom, such as a burning feeling and a persistent dryness. This condition is often worse as the day progresses, relieved by eating or oral activity and enhanced by stressful life events. Treatment starts by explaining to the patient that there is no disease or oral condition even though this seems to be the case and that the problem is with the 'feeling nerves' in the mouth. It is unclear whether there is a true local neuropathic problem in a dysaesthesia or whether it is an issue with the understanding and interpretation of the neural signals in the brain, as there is some experimental and treatment evidence for both. Very occasionally, similar symptoms can arise from mucosal atrophy as a result of haematinic deficiency and haematinics should be checked if a burning sensation is reported. Where sensory changes are reported, an MRI is a sensible precaution even if there are no cranial nerve deficiencies on testing. Occasionally, dysaesthesia symptoms can result from neuro-degenerative disease. Tricyclic antidepressants are the most effective treatment with nortriptyline having a better side effect profile than amitriptyline. Gabapentin and clonazepam have been used as alternatives. For mild cases, simple oral distractors such as chewing gum are useful. As these conditions are commonly associated with an underlying anxiety disorder, psychological intervention or hypnosis can be useful alternatives.

TEMPOROMANDIBULAR DISORDER

Temporomandibular disorders (TMD) encompass a range of pain and mechanical problems around the TMJ. Patients reporting locking of the joint or indicating pain only in the area of the joint itself have an internal joint derangement and require imaging and surgical assessment.

TMD represents the largest group of non-dental pains presenting in the head and neck. The actual presenting complaint varies from patient to patient but any diffuse head and neck pain which is chronic in nature must have TMD excluded. The core finding in TMD patients is a tendency to anxiety and as such they are a similar demographic to many other medical conditions including burning mouth syndrome, irritable bowel syndrome and fibromyalgia. Indeed, some view TMD as an extension of fibromyalgia to the head and neck with similar symptoms and management strategies.

Pain in TMD patients can be widespread and diffuse, affecting both sides of the face, head and neck or very focused on a single site, such as chronic midface pain, simulating dental pain in the molar teeth. It is characterized by an aching sensation which lasts for many hours or days at a time. In many cases, the pain centres around the masticatory muscles and the patient experiences limited mouth opening with pain when trying to chew. This can be accompanied by clicking of the TMJs and displacement

of the dental occlusion, all of which are compatible with the TMD pain syndrome diagnosis. Focal tenderness of the masticatory muscles is analogous to trigger points found in neck muscle pain or elsewhere in fibromyalgia. The clenching of teeth at night is a common finding in these patients but the muscle pain does not seem to be a direct consequence of this, as many patients clench their teeth and develop no chronic pain.

When the masticatory muscles are the focus for the patient's symptoms a plastic bite splint can be provided by the patient's dentist. If this is combined with a soft diet and supported yawning many patients will get good symptomatic relief. However, if the pain is more diffuse and chronic the use of a tricyclic antidepressant such as nortriptyline at night can aid recovery.

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CHAPTER 43

SALIVARY GLAND ANATOMY

Stuart Winter and Brian Fish

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SEARCH STRATEGY

Data in this chapter may be updated by a Medline search (as well as the websites Cancerlit and CancerNet) using the keywords: neck mass, head and neck neoplasm, imaging and fine-needle aspiration cytology, and focusing on diagnosis, surgery and management. The evidence in this chapter is mainly levels 3/4 with some level 2 evidence. The clinical recommendations are predominantly B and C.

INTRODUCTION

Embryogenesis and ultrastructure

The salivary glands share a common embryological development, whether they are the major named glands or the minor mucosal salivary glands.

The major salivary glands develop from the 6th to 8th weeks of gestation as outpouchings of oral ectoderm into the surrounding mesenchyme. The parotid develops first, growing in a posterior direction as the facial nerve advances anteriorly so that eventually, the parotid gland surrounds the facial nerve.

After the parotid glands are formed, the submandibular glands develop at 6 weeks and the sublingual glands at 8 weeks. The minor salivary glands arise from oral ectoderm and nasopharyngeal endoderm.

While the parotid is the first to develop, it is the last to become encapsulated, after the lymphatics develop. This results in entrapment of the lymphatics deep to the capsule in the parenchyma of the gland. Salivary epithelial cells can be included within these lymph nodes and this may be important in the development of Warthin's tumours and lymphoepithelial cysts within the parotid gland. The submandibular glands in general become encapsulated before lymphogenesis and usually do not have intraparenchymal lymph nodes.

The major glands lie distant to the oral mucosa, and are connected to the mucosa by excretory ducts. The minor glands lie within the mucosa or submucosa of the oral cavity and oropharynx and either open directly onto the surface of the mucosa or are connected to it via short excretory ducts.[1,2]

Microscopic anatomy

Salivary glands are made up of secretory acini and ducts. The acini can either be serous, mucous, or a mixture of serous and mucous. The secretory cells are categorized into three types. Cells containing small granules are serous and secrete salivary proteins and enzymes. Mucin-producing cells are cylindrical in shape and contain larger granules producing mucoproteins. Seromucinous cells have an intermediate ultrastructure.

The acinar ducts coalesce into intercalated ducts and subsequent striated ducts composed of columnar cells, before uniting into the main excretory duct of the gland.

The intercalated ducts are lined by simple low cuboidal epithelium, and surrounded by myoepithelial cells. The striated ducts have a folded basal membrane, enabling the active transport of substances out of the duct, such as water resorption and active secretion into the ducts. The excretory ducts are lined with a tall columnar epithelium.

Within the major salivary glands the acini are arranged into lobules and lobes within the glands. Each lobule has a single excretory duct. The lobules are linked by dense fibrous tissue containing excretory ducts, vessels, lymphatics, nerve fibres and ganglia to form lobes (**Figure 43.1**).

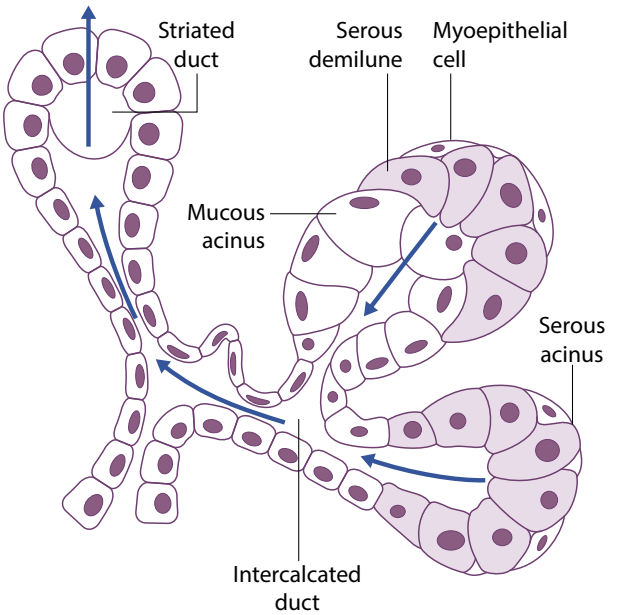

Figure 43.1 Part of a salivary gland showing a serous acinus and mixed serous-mucous acinus.

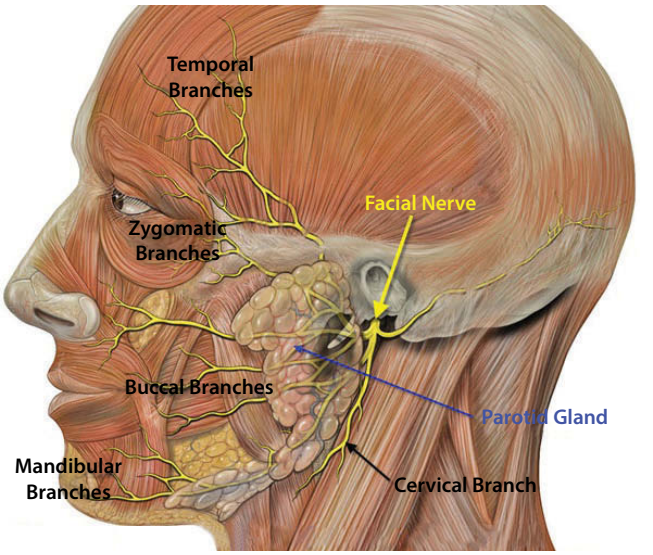

Figure 43.2 Anatomy of the parotid gland.

It is likely that the morphological description is an oversimplification and the products of these cells form an almost continuous series, from serous secretions with negligible amounts of protein-associated acidic carbohydrates, to mucous secretions rich in them.

THE PAROTID GLANDS

Clinical anatomy

The parotid glands are the largest of the salivary glands and are mainly serous, containing only a few mucous acini. Each gland weighs on average 25 g and is irregularly lobulated. It is wedge-shaped on coronal section and laterally extends from the zygomatic arch superiorly to the upper part of the neck inferiorly, where it overlies the posterior belly of digastric and the anterior border of the sternocleidomastoid muscle (**Figure 43.2**). Anteriorly it overlies the masseter muscle and posteriorly it extends below the external auditory canal and onto the mastoid process overlying the lateral process of C1. Medially it fills the gap between the mandible anteriorly the mastoid and the styloid process. It extends close to the lateral wall of the oropharynx and hence the need to examine the oropharynx when assessing the parotid gland (**Figure 43.3**).

The accessory parotid gland is a separate part of the gland usually lying on the masseter muscle between the parotid duct below and the zygomatic arch above.

The superficial (lateral) surface of the gland is concave and covered by the parotid fascia, skin and the posterior border of platysma. Some branches of the great auricular nerve lie superficial to the gland tissue and superficial lymph nodes lie on or deep to the fascia as well as within the gland. The great auricular nerve arises from the cervical plexus and provides sensation to the lower two-thirds of the pinna as well as to the parotid fascia and it is often possible to preserve at least its posterior branch during parotid surgery.

The anteromedial surface lies on the ascending ramus of the mandible and the medial pterygoid muscle as it inserts into the ramus. The gland is wrapped around the temporomandibular joint and joins the superficial surface over the masseter muscle to form the convex anterior border of the gland. The facial nerve and parotid duct emerge from this surface and run forwards deep to the anterior border. As the gland develops from the buccal cavity it grows backwards towards the ear. It envelops the external carotid artery, which divides into the maxillary and superficial temporal artery within the gland. The maxillary artery leaves the anteromedial surface and the superficial temporal artery continues superiorly to exit the gland from its superior surface. The auriculotemporal branch of the mandibular nerve runs deep to the superficial temporal vessels, passes within the capsule adjacent to the neck of the mandible and behind the temporomandibular joint.

The posteromedial surface lies on the mastoid process, the posterior belly of the digastric and the sternocleidomastoid muscles. Medially it overlies the styloid process with its attached muscles (styloglossus, stylohyoid and stylopharyngeus), which separate the gland from the internal carotid artery and internal jugular vein within the carotid sheath. This surface is indented by the external carotid artery prior to its entering the gland. The facial nerve trunk enters the gland high on the posteromedial surface between the mastoid and styloid processes.

Superficial to the maxillary and superficial temporal arteries lie the corresponding veins, which unite to form the retromandibular vein within the gland. The retromandibular vein emerges from the lower pole of the gland and divides into two branches. The anterior branch joins the facial vein before entering the internal jugular vein. The posterior branch joins the posterior auricular vein to form the external jugular vein. The division may occur within the gland and two branches emerge from the lower pole.

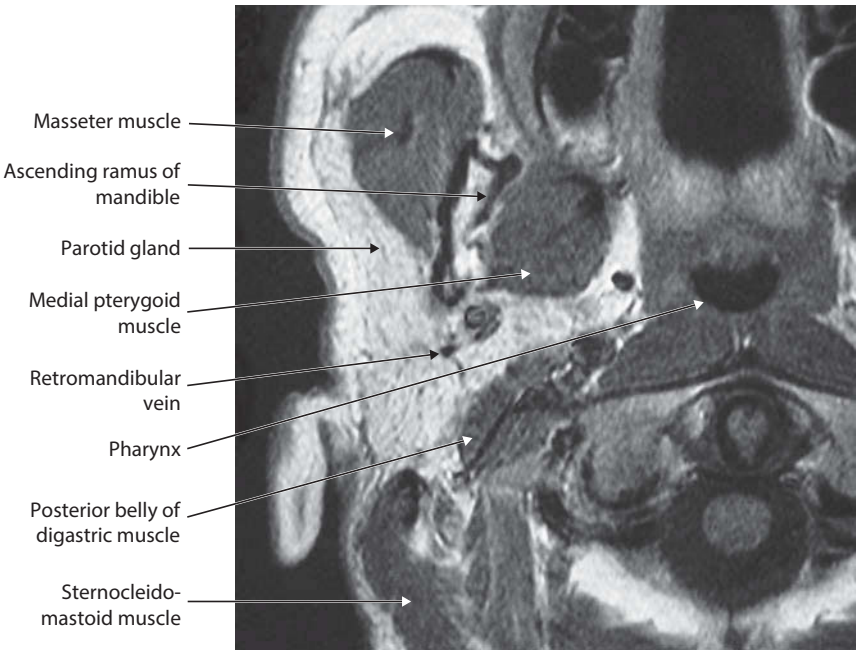

Figure 43.3 Axial MR scan showing the relationships of the wedge-shaped parotid gland, and its division into superficial and deep lobes by the retromandibular vein.

Once the facial nerve enters the gland it divides into two main temporal and cervical divisions. These pass forwards anteriorly dividing further before emerging from the anteromedial surface of the gland. The nerve divides the gland into superficial and deep lobes comprising approximately 80% and 20% of the gland respectively. The nerve lies superficial to the retromandibular vein, which is in turn superficial to the external carotid artery. The vein can be a useful radiological landmark for the nerve.

The capsule

The deep cervical fascia splits to surround the gland and is known as the parotid fascia. It is continuous anteriorly with the fascia covering the masseter as the parotidomasseteric and extends up to the zygomatic arch. Overlying the gland is the superficial musculoapneurotic system (SMAS). This is adherent to the parotidomasseteric fascia in the pretragal area and becomes separate from it as the fascia enters the cheek.[3] The deep part extends to the base of the skull and is thickened between the styloid process and the and the angle of the mandible forming the stylomandibular ligament.

The fascia is largely tough and inelastic but thins anteriorly. Inflammatory oedema pus and rapidly growing tumours contained within the capsule will cause it to stretch and become painful, often in advance of overt enlargement. The relatively thin fascia over the apex of the gland can lead to the spread of sepsis into the parapharyngeal space.

Most parotid tumours arise from the superficial lobe and expand towards the superficial surface but some deep lobe tumours are limited by the stylomandibular ligament and expand into the parapharyngeal space. Tumours arising from adjacent to the stylomandibular ligament may expand both ways to form a dumbbell-shaped mass.

The parotid duct

The parotid duct (of Stensen) is lined by low cuboidal epithelium surrounded by a smooth muscle and fibrous tissue wall. It originates within the gland, enveloped by the deep lobe of the parotid; only small ductules connect the superficial lobe with the duct.[4] It measures approximately 5 cm in length with an internal calibre of about 0.6 mm. It emerges from the anterior border of the parotid gland and travels across the masseter muscle. Having received the duct from the accessory gland it turns medially at the anterior border of the masseter. It pierces buccinator and runs obliquely between buccinator and the oral mucosa before entering the oral cavity at the parotid papilla opposite the second upper molar tooth. The facial nerve and its branches are always observed lateral to the parotid duct.

The surface marking is the middle of a line between the intertragal notch of the auricle and the midpoint of the philtrum, although a recent study suggests it may be lower than this.[5]

The facial nerve

The facial nerve emerges from the stylomastoid foramen just deep to the junction of the cartilaginous and bony parts of the external auditory meatus, usually as a single trunk but rarely as a double trunk. This has been estimated at 3–26.7%. Similar anomalies have been documented in the intratemporal course of the nerve, often associated with other congenital abnormalities. The existence should therefore be especially considered in patients with congenital abnormalities of the pinna or with congenital hearing loss. The main trunk lies approximately 1 cm above the posterior belly of the digastric muscle and it passes downwards and forwards over the styloid process and attached muscles before entering the substance of the gland. This part of the nerve gives off the posterior auricular branch,

which passes upwards to supply the occipital belly of occipitofrontalis, and a muscular branch, which divides to supply the posterior belly of the digastric and the stylohyoid muscles.

On entering the substance of the gland the main trunk divides into upper zygomaticotemporal and lower cervicofacial divisions. Further subdivisions then occur to form five branches – temporal, zygomatic, buccal, mandibular and cervical – supplying the muscles of facial expression. The resulting pattern is known as the pes anserinus. The branching pattern is variable and a number of classifications have been described. McCormack et al. and Davis et al. both described six patterns.[6, 7] Katz and Catalano[8] described five patterns (**Figure 43.4**) and Kwak et al. four, based on the origin of the buccal branch.[9] The cross-innervation between branches and divisions of the facial

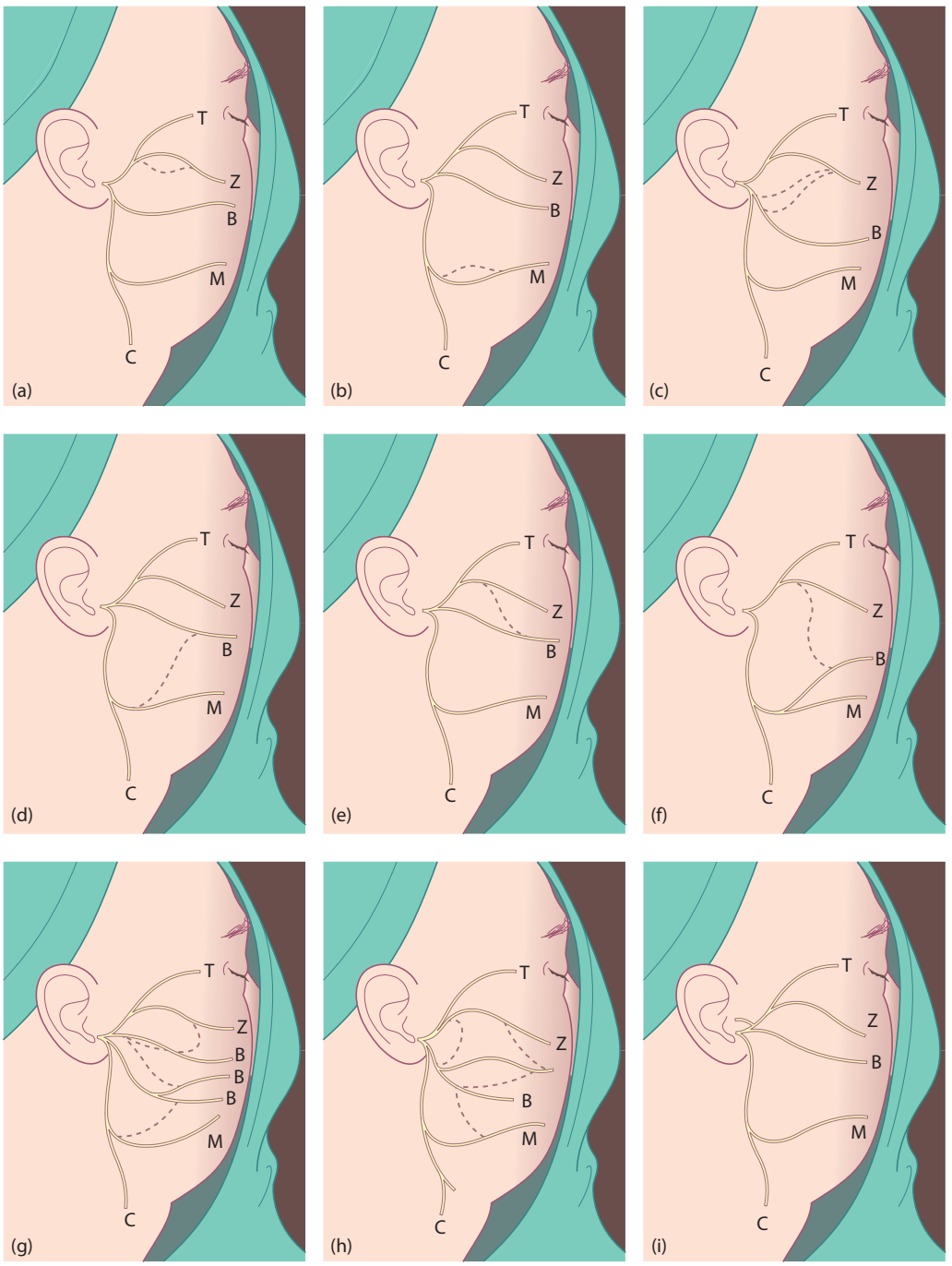

Figure 43.4 Intraparotid branching patterns of the facial nerve. **(a)** and **(b)** Type 1: in this type there is splitting and subsequent reunion of the zygomatic or mandibular branches. **(c)** Type 2: in this type subdivisions of the buccal branch fuse with the zygomatic branch peripherally. **(d)**, **(e)** and **(f)** Type 3: in this type there are major communications between the buccal branch and others. **(g)** and **(h)** Type 4: there are complex branching and anastomotic patterns between the major divisions in this type. **(i)** Type 5: in this type the facial nerve leave the skull as more than one trunk. B, Buccal branch; C: cervical branch; M, mandibular branch; T, temporal branch; Z, zygomatic branch.

nerve is most pronounced between zygomatic and buccal branches and least for the marginal mandibular branch. This explains why significant defects in midfacial movement are rarely seen following injury to the buccal or zygomatic branches and are relatively common following a marginal mandibular injury. An understanding of the variability is essential for those undertaking parotid surgery (see **Figure 43.2**).

Nerve supply

Preganglionic secretomotor fibres are carried from the inferior salivatory nucleus in the medulla along the glossopharyngeal nerve, its tympanic branch, the tympanic plexus and the lesser petrosal nerve to the otic ganglion. Post-ganglionic fibres are carried to the gland via the auriculotemporal nerve.

Sympathetic (vasoconstrictor) fibres are carried to the gland via the plexus on the external carotid and middle meningeal arteries from the superior cervical ganglion.

The gland receives sensory fibres from the auriculotemporal nerve and the fascia receives its sensory innervation from the great auricular nerve (C2).

Vessels

Branches of the external carotid artery supply the gland. Venous drainage is via the retromandibular vein into the external and internal jugular veins.

THE SUBMANDIBULAR GLANDS

The submandibular glands are the second largest of the major salivary glands. They consist of a larger superficial part and a smaller deep part wrapped around the posterior border of mylohyoid. The gland lies in the submandibular triangle formed by the anterior and posterior bellies of the digastric muscle and the inferior margin of the mandible. Each is irregular in shape and weighs 7–16 g.[1]

The lateral surface lies adjacent to the body of the mandible in the mandibular fossa and the origin of the medial pterygoid. The facial artery enters or deeply grooves the gland posteriorly, after emerging from deep to the superior margin of the posterior belly of the digastric. It initially lies deep to the gland before turning anterolaterally to emerge between the gland and the lower border of the mandible.

The superficial part is covered by skin, platysma and a fibrous capsule, derived from the deep cervical fascia. The capsule runs from the greater cornu of the hyoid bone and splits to enclose the gland before blending with the periostium of the mandible along the mylohyoid line medially, and the lower border of the body of the mandible laterally. The fascia is crossed by the facial vein, the cervical branch of the facial nerve and the marginal mandibular branch of the facial nerve.

The medial surface lies on the surface of mylohyoid anteriorly, with the nerve to mylohyoid and submental vessels. Posteriorly the gland overlies hyoglossus, the lingual nerve with its submandibular ganglion, hypoglossal nerve, stylohyoid and posterior belly of the digastric.

The deep part of the gland lies between mylohoid and hyoglossus. It lies between the lingual nerve above and the hypoglossal nerve below.

The submandibular duct

Like the parotid duct, the submandibular duct is approximately 5 cm long. It is formed by the coalescence of numerous ducts within the superficial part of the gland before emerging from the medial surface of this part of the gland, traversing the deep part before running anteriorly along the floor of the mouth between mylohyoid and hyoglossus. It emerges on the summit of the sublingual papilla adjacent to the lingual frenulum after passing between the sublingual gland and genioglossus. Whilst running forwards on hyoglossus, it lies between the hypoglossal and lingual nerves. The lingual nerve crosses the duct laterally at the anterior edge of hyoglossus before branches of the nerve emerge on the medial surface of the duct (**Figure 43.5**).

The size of the duct varies between ducts and along its length. The duct is narrowest at the ostium. In one study the mean duct diameters ranged between 1.5 mm and 0.5 mm.[10, 11]

Vessels and nerves

The arterial blood supply is from the submental branch of the facial artery, a branch of the external carotid.

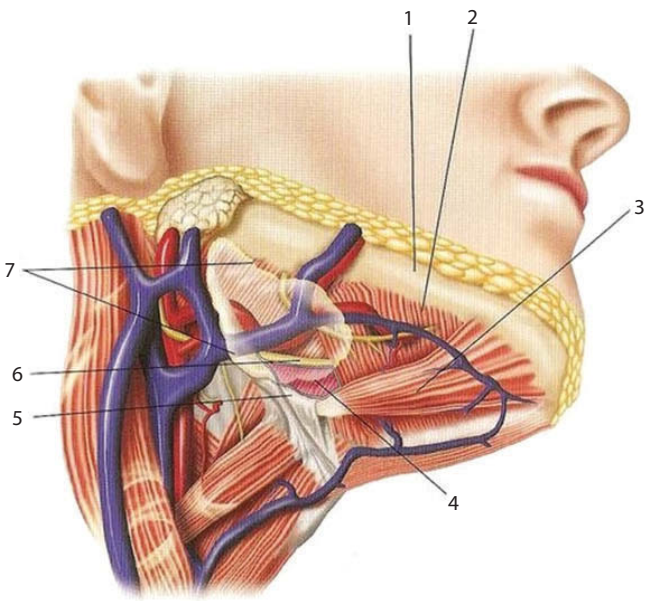

Figure 43.5 Submandibular glands. 1. Mandible. 2. Mylohyoid. 3. Anterior belly of digastric. 4. Submandibular gland. 5. Hyoid. 6. Hypoglossal nerve. 7. Facial artery.

The venous drainage is into the corresponding facial vein. An important anatomical relationship is that the marginal mandibular nerve passes lateral to the vein and, therefore, dissecting deep to the vein, can be used to preserve or identify the nerve.

The submandibular lymph nodes lie adjacent at the medial aspect and anterior end of the superficial part and sometimes within the gland itself. Lymphatics drain into the deep cervical group, particularly the jugulo-omohyoid nodes.

The sympathetic innervation of the gland is from the superior cervical ganglion via the lingual artery. Presynaptic parasympathetic innervation is via the lingual nerve, a branch of the mandibular division of the Vth cranial nerve to the submandibular ganglion. Innervation is initially from the superior salivatory nucleus in the pons passing through the nervus intermedius and carried by the chorda tympani nerve.

Lymphatic drainage goes to the deep cervical and jugular chains of nodes. Perivascular lymph nodes near the facial artery are often involved with cancer originating in the submandibular gland, and these nodes should be removed with submandibular resection.

THE SUBLINGUAL GLANDS

The sublingual glands are the smallest of the paired named salivary glands and unlike the other major salivary glands have no true fascial capsule. Almond-shaped, they lie beneath the mucosa of the floor of the mouth, between the mandible and genioglossus muscle and inferiorly they are bounded by the mylohyoid. The submandibular duct (Wharton's) and the lingual nerve pass between the sublingual gland and genioglossus muscle. Each weighs approximately 4 g.

There is no dominant duct drainage and most of the small excretory ducts (ducts of Rivinus) open directly on the summit of the sublingual fold, but some may open into the submandibular duct itself (Bartholin's duct).[1]

Vessels and nerves

The blood supply is via the sublingual and submental vessels, branches of the lingual and facial vessels. Innervation is similar to the submandibular gland, with sympathetic innervation from the cervical chain ganglia and the parasympathetic supply via the submandibular ganglion.

Lymphatic drainage goes to the submandibular nodes.

KEY POINTS

- The intraparotid portion of the facial nerve has a variable branching pattern.
- The anatomy of the fascial capsules of the salivary glands influences the spread of salivary gland disease.

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CHAPTER 44

PHYSIOLOGY OF THE SALIVARY GLANDS

Mriganke De and T. Singh

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SEARCH STRATEGY

Data in this chapter may be updated by a Medline search using the following keywords: salivary glands; saliva; production; constituents; pathophysiology of saliva.

INTRODUCTION

Salivary glands produce saliva, which plays an important role in the maintenance of oral health. The largest portion of total saliva volume is produced by three paired major salivary glands: the parotid, the submandibular and the sublingual salivary glands. In addition, there are 600–1000 minor salivary glands present in the mucosal lining of the oral cavity and oropharynx that also contribute to total saliva production.[1] Each pair of glands produces saliva of differing consistency. This variation of consistency depends on several factors including blood flow to the gland, which in turn correlates with volume of saliva produced initially. Further modification of saliva properties results from post-secretion modifications that occur within the salivary gland duct unit.

MICROANATOMY OF SALIVARY GLANDS

The secretory unit of a salivary gland consists of the acinus, enveloped by myoepithelial cells, and distally in order away from the acinus, the intercalated duct, the striated duct and the excretory duct (**Figure 44.1**).

The acinus

All acinar cells contain secretory granules, but the secretory product of acinar cells varies between salivary gland types and this is reflected in the different intracellular secretory granules.

In serous glands, the acinar cells are rich in protein (amylase) secreting granules. In contrast, mucous salivary glands are rich in secretory granules, which contain mucin. The relative abundance of secreting granules in the acinar cells dictates the consistency and composition of the secreted saliva.

Three types of acinus have been described:

- Serous (protein-secreting) – spherical cells rich in zymogen granules
- Mucous (mucin-secreting) – tubular shaped cells; mucin granules are washed out on haematoxylin and eosin preparations giving an empty cell appearance
- Mixed – varying proportions of serous and mucous acinar cells.

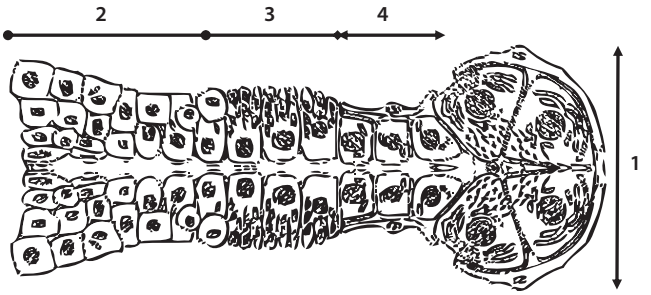

Figure 44.1 Basic salivary duct unit.

Within the acinus, the acinar cells and the cells of the proximal ductal system (intercalated duct) are enveloped by pseudopodia of surrounding myoepithelial cells. They have contractile properties and create the peristalsis action which moves saliva away from the acinus, distally along the salivary duct system.

The lumen of the acinus communicates directly with the lumen of the duct. As seen in **Figure 44.1**, the ductal system, from proximal to distal, comprises the intercalated duct, striated duct and excretory duct.

The intercalated duct

The intercalated duct is lined by low cuboidal epithelial cells rich in carbonic anhydrase. As a consequence, these cells secrete bicarbonate into the lumen and absorb chloride from the lumen. Therefore the intercalated ducts modify saliva composition produced by the acinar cells as it passes to the striated duct. This part of the duct is short and poorly developed in mucinous salivary glands.

The striated duct

The striated duct is lined by simple cuboidal cells that exhibit extensive folding of basal and basolateral plasma membrane. The folds are associated with numerous mitochondria. These cells absorb sodium from the lumen and secrete potassium into the lumen, thereby producing increasingly hypotonic fluid. The faster the salivary flow rate and/or the longer the striated duct, the more alteration of saliva composition will result. Not surprisingly, therefore, striated ducts are short or even non-existent in mucous secreting salivary glands, resulting in minimal or no modification of saliva composition. In contrast, these ducts are well developed in serous glands, resulting in heavily modified salivary composition.[2]

The excretory duct

Excretory ducts are lined by simple cuboidal epithelium proximally and striated cuboidal or pseudostratified columnar epithelium distally. These cells do not perform any modification to the salivary content.

The composition of the duct unit, including the relative abundance of mucin-secreting or protin secreting acinar cells, together with the length of the intercalated and striated ducts, dictate the salivary gland phenotype.

Accordingly the parotid gland is a serous salivary gland with the mucinous to acinar cell ratio 1:1 in the parotid acini. The submandibular glands are mixed but produce predominantly serous saliva. In contrast, the sublingual glands, which are also mixed glands, produce predominantly mucinous saliva.

In addition to the ductal microanatomy, the salivary gland stroma is rich in lymphocytes and plasma cells, which are responsible for the production of IgA, which is secreted into the salivary duct system to be excreted in the saliva.[3]

PHASES OF SALIVARY SECRETION

The production of saliva is an active process occurring in two phases:

1. Primary secretion is produced by the acinar cells and is an active process; the result is a product similar in composition and osmolality to plasma.
2. The primary secretion is then modified as it passes down the ductal system, again by active processes occurring in the cells lining the duct. Broadly, as the primary secretion passes down the duct the primary secretion becomes progressively more hypotonic with decreased sodium and increased potassium concentrations.

In general, saliva comprises 99.5% water, in addition to proteins, glycoproteins and electrolytes. The saliva is high in potassium (7x that of plasma), low in sodium (1/10x that of plasma,) calcium, phosphorous, chloride, thiocyanate, and urea resulting in a pH of 5.6–7.[4]

SALIVARY PHYSIOLOGY

The functions of saliva and the associated individual components are detailed in **Table 44.1**.

SALIVARY FLOW

The average volume of saliva secreted from the major salivary gland in a 24-hour period is 1–1.5 litres (**Figure 44.2**). Secretion from the major glands is inducible and most saliva is secreted during mastication. The basal salivary flow rate is 0.001–0.2 ml/minute/gland, while the stimulated salivary flow rate increases to 0.18–1.7 ml/minute/gland. In contrast, the salivary flow from the minor salivary glands is independent of stimulation and constitutes 7–8% of total salivary output. The saliva produced by minor salivary glands is rich in mucin and is primarily responsible for maintaining oral mucosal lubrication.[1]

In an unstimulated state the contribution of measured salivary gland is:

- submandibular gland: 69%
- parotid gland: 26%
- sublingual gland: 5%.

TABLE 44.1 The major functions of saliva

Function		Responsible component
Oral protection	• Lubrication • Antimicrobial • Growth factors • Mucosal integrity • Lavage/cleansing • Buffering • Remineralization	• Mucins, proline-rich glycoproteins, water • Amylase, complement, defensins, lysozyme, lactoferrin, lactoperoxidase, mucins, cystatins, histatins, proline-rich glycoproteins, secretory leukocyte protease inhibitor, statherin, thrombospondin • EFG, TGF-$_x$,TGF-β, FGF, IGF-1 and IGF-2, NGF • Mucins, electrolytes and water • Water • Bicarbonate, phosphate ions, proteins • Calcium, phosphate, statherin, anionic proline-rich proteins
Digestion and speech production	• Alteration of food constituency • Digestion • Taste (Food solute) • Speech (oral cavity lubrication)	• Water, mucins • Amylase, lipase, ribonuclease, proteases, water mucins • Water, gustin • Water, mucins

EGF, epidermal growth factor; FGF, fibroblast growth factor; IGF1 and IGF2, insulin-like growth factor; NGF, nerve growth factor; TGF-α, transforming growth factor-alpha; TGF- β, transforming growth factor-beta.

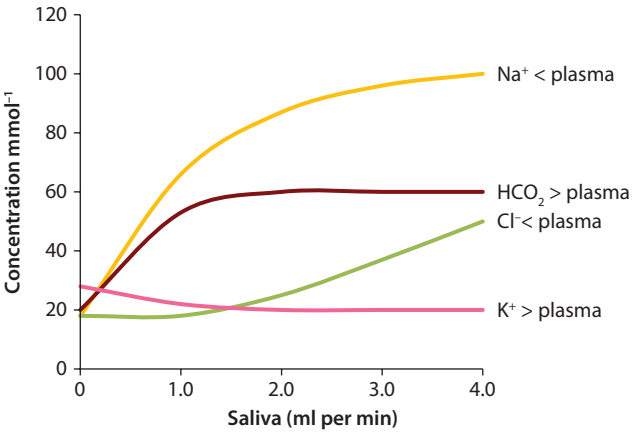

Figure 44.2 Salivary flow rates and changes in ionic composition.

In a stimulated phase the relative contributions of major salivary glands are:

- parotid gland: 69%
- submandibular gland: 26%
- sublingual gland: 5%.

THE AUTONOMIC NERVOUS SYSTEM AND SALIVARY SECRETION

The normal secretion of saliva depends on a centrally coordinated balance of sympathetic and parasympathetic activity. Parasympathetic activity, which is typically tonic, provokes most of the secretion by stimulating exocytosis from the secretory cells and varying the extent of vasodilatation of blood supply of the individual gland as well as stimulating the contraction of myoepithelial cells surrounding the gland acinus and proximal ductal system. In contrast to the tonic stimulation of the parasympathetic system, the sympathetic stimulation tends to be more intermittent and acts in opposition to the parasympathetic input. It is, however, able to modulate the composition of saliva by varying the exocytosis from specific cells lining the duct system.

It follows that the parasympathetic nervous system is the primary instigator of salivary secretion. Interruption of parasympathetic supply to the salivary glands results in glandular atrophy while interruption of sympathetic supply results in no significant change in the gland architecture.

The secretomotor cholinergic parasympathetic fibres for the parotid gland originate in the inferior salivatory nucleus. Fibres travel via the glossopharyngeal nerve initially and then via the lesser superficial petrosal nerve to synapse in the otic ganglion. The post-ganglionic fibres reach the gland through the auriculotemporal nerve. In contrast, the parasympathetic fibres of the submandibular and sublingual glands originate in the superior salivatory nucleus and travel via the hypoglossal nerve originally and then via chorda tympani to the submandibular ganglion; the post-ganglionic fibres release acetylcholine in close proximity to the glands with no true post-ganglionic synapses. In comparison, the adrenergic post-ganglionic sympathetic fibres travel from the superior cervical ganglion in fibres that pass along the external carotid artery and its branches, to reach the glands.[1]

MECHANISMS OF SALIVARY SECRETION

The mechanisms of saliva secretion have been reviewed in detail by Baum.[5] Most of the information presented below comes from the study of rat salivary glands. Little is known of the mechanisms of human salivary secretion, but similarities are assumed to exist in the physiology of salivary secretion across species.

Saliva is produced in response to neurotransmitter stimulation. Both the adrenergic and cholinergic systems have a role in the salivary secretion. Neurotransmitters bind to relevant receptors in the basolateral region of the acini. Noradrenaline, whether from the sympathetic system or circulating following release from the adrenal glands, binds to both α- and β-adrenergic receptors, while parasympathetic derived acetylcholine binds to cholinergic receptors. Secondary message pathways of both types of

receptor depend on guanine nucleotide-binding regulatory protein (G protein) for transduction of the neurotransmitter stimuli. The G proteins that transduce signals following binding of neurotransmitter to the receptors of acinar cells are heterotrimeric molecules consisting of α, β and ɣ subunits. The α subunit is the site of guanine nucleotide binding and probably confers the functional specificity of a given G protein. Binding of a neurotransmitter to a receptor results in conformational change of the intracytoplasmic portion of the receptor, which facilitates association of a G protein. Binding of the G protein provokes replacement of GDP by GTP at the G protein nucleotide binding site and promotes dissociation of the heterotrimer into a free α subunit and a βɣ heterodimer. The resulting GTPase activation of the α subunit catalyzes the hydrolysis of GTP to GDP. The GDP bound to the α subunit then re-complexes with the βɣ complex to restore the original heterotrimeric molecule.

The G protein signal transduction pathways propagate to result ultimately in the generation of cAMP as a result of β adrenergic receptor stimulation and formation of 1,4,5-inositol triphosphate (IP_3) after acetylcholine receptor stimulation. The specific mechanism by which cAMP results in protein exocytosis into saliva remains unclear. However, in rat salivary glands, β-adrenergic receptor stimulation leads to a rise in cAMP levels, and amylase or glycoprotein secretion by the parotid or submandibular glands, respectively.

IP_3 activity is known to result in an influx of extracellular calcium into the acinar cell cytoplasm. The exact mechanism for this effect is unclear, although it has been established that this effect is not voltage activated.

Possible mechanisms for Ca^{++} entry into acinar cells include a direct receptor (IP_3)-gated Ca^{++} channel, a G protein activated Ca^{++} channel or a second messenger activated Ca^{++} channel, but the existence of any of these has yet to be established, although there is some evidence suggesting the synergistic action of IP_3 and its metabolite 1,3,4,5-inositol tetrakisphosphate (IP_4) is important in promoting Ca^{++} influx.

Currently, the most favoured explanation of the mechanism of Ca^{++} entry is termed Capacitative Ca^{++} entry. By this mechanism, dynamic depletion of the intracellular Ca^{++} storage pool provides the concentration gradient that drives sustained Ca^{++} entry. Support for this theory comes from experimental data that show that graded depletion of the Ca^{++} store (using for, for example, the ER uncoupler thapsigargin) have led to similarly graded Ca^{++} entry. Despite this hypothesis, the mechanism of continued depletion of intracellular Ca^{++} is, to date, not established. What is known is that extracellular pH and cytoplasmic Ca^{++} do modulate extra to intracellular Ca^{++} flux.

Acinar cells are water permeable and therefore able to derive fluid from the surrounding blood vessels, the movement of which is, in turn, determined by the vasodilation of the gland microcirculation as well as osmotic and hydrostatic pressure gradients. Whilst acinar cells are permeable the salivary duct system in impermeable to water. That said, active transport processes in the plasma membranes of the cells lining the duct, which result in the removal of sodium and chloride and the addition of potassium and bicarbonate ions as well as proteins, are able to modify the composition of the saliva as it passes along the duct.

MECHANISMS OF ION TRANSPORT IN SALIVARY ACINI

As in all secretory epithelia, fluid transport in salivary gland cells is thought to be driven osmotically by transepithelial concentration gradients. Studies on rat and rabbit salivary glands have suggested three mechanisms that act concurrently resulting in the production of primary salivary fluid secretion.[6]

The first mechanism depends on the combined action of four membrane transport systems (see **Figure 44.3**), namely:

1. a Na^+ -Cl^- co-transporter that is located in the basolateral membrane of the acinar cells
2. a basolateral Ca^{++}-activated K^+ channel (not shown in **Figure 44.3**)
3. an apical conductive pathway for Cl^-, which is presumably a Ca^{++} -activated Cl^- channel
4. a basal Na^+/K^+ ATPase.

In the resting state, K^+ and Cl^- concentration gradients, where the intracellular concentration exceeds the extracellular concentration, are actively created by by a Na^+/K^+ ATPase and a Na^+/K^+ - $2Cl^-$ cotransporter respectively.

Secretory stimulation via the parasympathetic nervous system, as described above, leads to a rise in intracellular Ca^{++} concentration, which, in turn, results in the opening of the basolateral K^+ channel and the apical Cl^- channel.

K^+ and Cl^- then flow along their respective concentration gradients – K^+ into the ECS and Cl^- into the duct lumen – resulting in the accumulation of Cl^- ions into the primary salivary fluid. A consequence of this is a net negative charge of the primary salivary fluid, which promotes the transport of sodium ions from the interstitium into the duct lumen. The resulting osmotic gradient for NaCl, in turn, provokes the transepithelial movement of water from the interstitium to the lumen.

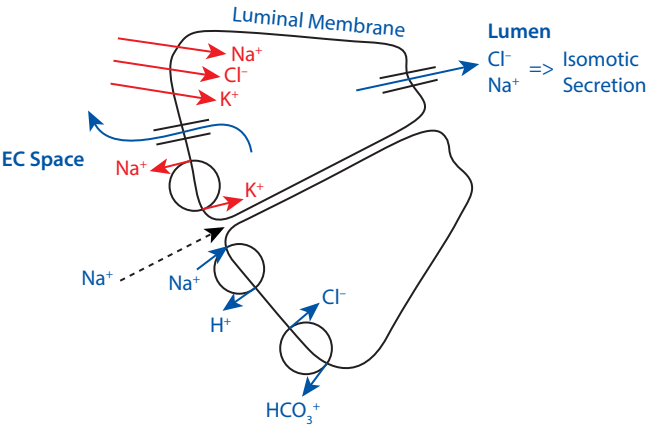

Figure 44.3 The ion exchange that occurs at the salivary acinus via the anion exchange pumps located on the basal and luminal surface of the salivary acinus.

Continued parasympathetic input results in continued transepithelial chloride flux and increased saliva volume. Cessation of parasympathetic stimulus is followed by a fall in intracellular calcium concentration to resting levels, closure of the K^+ and Cl^- channels and the return of the cell to its resting state.

The second mechanism also involves the creation of an intracellular Cl^- concentration gradient. However, in this case this is created by a Cl^-/HCO_3 exchanger acting in tandem with a Na^+/H^+ exchanger. A fall in intracellular chloride concentration as a result of parasympathetically stimulated KCl loss thus leads to entry of more Cl^- in exchange for HCO_3^-. Acidification of the cytoplasm that results from this bicarbonate loss is buffered by the Na^{++}/H^+ exchanger, which uses the extracellular-to-intracellular sodium gradient generated by Na^+/K^+ ATPase, to drive protons out of the cell.

Unlike the first two mechanisms in which chloride is the secreted ion, the third involves active bicarbonate secretion. CO_2 enters the acinar cell across the basolateral membrane and is converted to HCO_3^-, which is lost across the apical membrane via an anion channel, which is possibly the same as the Cl^-/HCO_3 exchanger involved in chloride secretion as described in second mechanism above. Acidification is rectified by the expulsion of a proton by the basolateral Na^+/H^+ exchanger.

FACTORS AFFECTING SALIVARY FLOW

Xerostomia is the term used to describe reduced salivary flow.[7–9] Xerostomia may be subjective or objective. In the former a reduction in saliva is perceived, while in the latter a genuine reduction in saliva flow is detectable. For example, Ship et al. found that, although xerostomia is a common symptom in postmenopausal women, no actual reduction of saliva flow in otherwise normal women is detectable.[7]

In clinical practice, drugs are the most common cause of measurable decreased salivary gland function. **Table 44.2** shows a list of drugs that commonly may affect salivary secretion. Not surprisingly, most of these drugs possess anti-cholingeric or sympathomimetic effects, mechanisms that are known to be essential for normal saliva production. Tricyclic antidepressants and phenothiazine neuroleptics are among the most troublesome as they have particularly strong anticholinergic (antimuscarinic) effects. Ganglion-blocking drugs can also have a similar effect.

Xerostomia may also result from specific disease states that do not involve specific salivary gland pathology. For example, depression and anxiety states and their attendant bystander anticholinergic side effects of the underlying condition may result in measurable xerostomia. Busfield et al. measured the rate of salivary secretion in 42 untreated depressed patients and found it to be decreased in comparison to non-depressed hospital patients and healthy controls. However, there is no relationship between the degree of xerostomia and the severity of depression.[8, 9]

Moreover, xerostomia is an inevitable consequence of dehydration induced by, for example, haemorrhage, diarrhoea, chronic vomiting, polyuria secondary to diabetes and restricted fluid intake or overdose of diuretics.

COLLECTION OF SALIVA

Measuring salivary flow rate facilitates a diagnosis of xerostomia – however, accurate measurement of flow rate is not a trivial matter. Usually, the collection of saliva is performed under three circumstances:

- Unstimulated flow of total saliva
- Stimulated flow of total saliva
- Stimulated or unstimulated flow of an individual gland.

Systemic or local sialagogues may be used to stimulate flow. The archetypal systemic salivary sialagogue is pilocarpine, a parasympathomimetic, although this is rarely used outside research. Local sialagogues are more convenient, with minimal side-effect profiles and are therefore used more commonly in the clinical setting. A commonly used protocol involves the dropwise application of 5% citric acid solution on the dorsum of the tongue. As for collecting saliva, a variety of methods are used. These include spitting, drainage, suction and cotton wool rolls. The particular method used is determined by whether global or individual gland salivary output is the desired endpoint.

For example, saliva produced exclusively by the parotid gland is accurately collected by cannulating the parotid duct with a polythene catheter. Alternatively, a Carlson-Crittenden cup could be used. This device is specifically

TABLE 44.2 Drugs liable to cause xerostomia

Drugs with anticholinergic activity	Drugs with sympathomimetic activity
• Atropine and analogues (hyoscine, ipratropium, etc.) • Tricyclic antidepressives • Monoamine oxidase inhibitors • Phenothiazines and related neuroleptics • Orphenadrine, benzhexol and related anti-Parkinsonian agents • Antihistamines • Ganglion blockers and clonidine • Antiemetics (antihistamines, hyoscine and phenothiazines)	• 'Cold cures' and decongestants containing ephedrine or phenylpropylamine • Bronchodilators (isoprenaline, orciprenaline, etc.) • Appetite suppressants, particularly amphetamines and diethylpropion

designed for the task and involves a collecting chamber that is placed on the buccal mucosa over the ampulla of the duct, which is separated from an outer suction chamber, which ensures that the saliva produced is sucked into the collecting chamber.

Saliva produced by the submandibular and sublingual glands is typically collected using a syringe. Individual gland production is technically impossible due to the close proximity of duct orifices in the anterior floor of mouth or more pertinently by the numerous potential communicating channels between the duct systems of all four glands.

The choice of method used depends on the type of investigation being carried out. In clinical practice, for example in the diagnosis of Sjögren's syndrome, measurement of total salivary flow in the presence and absence of stimulation over a period of 10–15 minutes where saliva is collected by the patient spitting, usually suffices.[10]

SIALOCHEMISTRY

Saliva chemistry may also change in disease and therefore, the chemical composition of normal saliva is an important reference point (**Table 44.3**).

SALIVARY PHYSIOLOGY IN DISEASE

Examples of changes in the concentration of inorganic ions and organic components in saliva in diseased states are shown in **Tables 44.4** and **44.5** respectively. Low flow states, the development of local inflammation and cellular calcified nidi may promote salivary debris (sludge) and calculi formation.

Three diseases that have been studied in terms of sialochemistry in particular detail are Sjögren's syndrome, cystic fibrosis and coeliac disease.

Sjögren's syndrome

The European Community Study Group on Diagnostic Criteria for Sjögren's Syndrome concluded that unstimulated whole saliva flow rate and minor salivary gland biopsy are the two most valuable diagnostic tests. A low resting as well as stimulated flow rate are typical of Sjögren's syndrome. The cut-off values of 0.1 mL/min for resting whole saliva and 0.5 mL/min for stimulated saliva has been considered diagnostic of salivary gland hypofunction and consistent with a diagnosis of Sjögren's syndrome.

Cystic fibrosis

Cystic fibrosis is an autosomal recessive genetic condition that affects 1 in 3000 newborns of Northern European ancestry. Affected individuals are homozygous for mutations of the cystic fibrosis transmembrane conductance regulator (CFTCR) gene. The CFTCR is responsible for regulating chloride ion transport across cell membranes. The net effect of its absence is the formation of exocrine secretions of increased viscosity. That said, the effect on total saliva production is minimal. However, significant

TABLE 44.3 Composition of mixed saliva

	Unstimulated		Stimulated	
Substance	**Mean + s.d.**	**Range**	**Mean + s.d.**	**Range**
Protein (g/L)		1.4–6.4	2.8	1.8–4.2
IgA (mg/L)	194.0			
IgG (mg/L)	14.4			
IgM (mg/L)	2.1			
Amylase (g/L)	0.38 + 0.08			
Lysozyme (mg/L)			108.9 + 29.1	3.7–625
Carbonic anhydrase (K/L)			2100	
Histamine (mg/L)	0.15	0.11–0.18		
Glucose (mmol/L)	0.55 + 0.048		0.056	0.02–0.17
Urea (mmol/L)	3.22 + 2.5	2.33–12.5	2.17	0.1–4.8
Creatinine (mg/L)	0.09	0.04–0.18		
Cholesterol (mg/L)	0.2	0.07–1.3		
Sodium (mmol/L)	6.2 + 0.46		26.4 + 11.8	
Potassium (mmol/L)	21.6 + 1.2		19.7 + 3.9	
Calcium (mmol/L)	1.56 + 0.06		1.48 + 0.04	
Magnesium (mmol/L)	0.21 + 0.01		0.15 + 0.04	
Phosphate (mmol/L)	6.2			
Chloride (mmol/L)	17.4 + 1.4		29.0 + 8.8	
Iodide (umol/L)	0.8	0–3		1–3
Fluoride (umol/L)	1.5 + 0.68	0.5–3	0.56 + 0.25	0.25–1.2

TABLE 44.4 Changes in the concentration of inorganic ions

Condition	Changes in the concentration of inorganic ions
Sialadenitis	Raised Na^+ , K^+, Ca^{++} and P^+ levels
Radiation damage	Raised Na^+, Ca^{++}, Mg^{++} and Cl^- levels
Sjögren's syndrome	Raised Na^+, Cl^- and P^+ in parotid gland saliva
Cystic fibrosis	Raised Na^+, Ca^{++} and P^+ levels. Mandel[10] suggested that the combined Ca^{++} and P^+ concentrations formed a useful diagnostic index
Aldosteronism	Depressed Na^+ but raised K^+ levels. Mandel[10] suggested that the product Na^+/K^+ could form a useful diagnostic index
Hypertension	Depressed Na^+ levels
Alcoholic cirrhosis	Raised K^+ levels
Hyperparathyroidism	Raised Ca^{++} levels
Diabetes mellitus	Raised Ca^{++} levels
Chronic pancreatitis	Depressed HCO_3^- levels
Psychiatric illness	Possibly raised Na^+ levels
Digitalis intoxication	Raised Na^+ and K^+ levels. Mandel[10] suggested that the product, Na^+ x K^+, could form a useful diagnostic index

TABLE 44.5 Conditions affecting the composition of saliva

Condition	Effect on composition of saliva
Sjögren's syndrome	Raised total protein and β_2 microglobulin levels in parotid gland saliva
Cystic fibrosis	Raised total proteins, amylase, lysozyme in submandibular gland saliva and glycoproteins in parotid gland saliva
Cirrhosis	Raised total protein and amylase in parotid gland saliva
Hyperparathyroidism	Raised total protein
Diabetes mellitus	Raised total protein, IgA, IgG and IgM and raised glucose levels
Sarcoidosis	Depressed amylase and lysozyme levels

changes in the salivary chemistry result in a dramatic elevation in the salivary protein and calcium concentrations. The net effect is a predisposition to salivary duct blockage and an increased frequency of salivary calculi, particularly of the minor salivary glands, resulting in a build-up of calculi around the gingival margins.

Coeliac disease

This condition is characterized by malabsorption of gluten in the intestines. One can detect antibodies (IgA–AGA) to gliadin, a major component of gluten, in saliva and serum. Consequently, salivary serology can be used as a screening test for coeliac disease although it lacks the sensitivity of its serological counterpart.[11]

SIALOLITHIASIS

A deleterious increase in the viscosity of saliva (through, for example, dehydration), reduced flow or even stasis, by mucosal obstruction or inflammation of the lining of the salivary unit with retention of cellular or bacterial debris, may precipitate liathiasis (stone formation) and painful salivary obstruction. The biochemical components of salivary stones vary depending on the gland, as do their resulting imaging appearances (for example, due to the relative calcium composition, 90% of parotid stones are radiolucent whilst 90% of submandibular stones are radio-opaque).

THE EFFECT OF CHEMOTHERAPY AND RADIOTHERAPY

Saliva is critically important for dental hygiene and maintenance. Due to the high turnover of the salivary duct unit component cells, these areas are at extreme vulnerability from bystander tissue effects of ionizing radiation and chemotherapeutic agents. Profound xerostomia is therefore the most common short- and long-term adverse event of non-surgical treatment of cancers of the head and neck. The resulting xerostomia has a profound negative impact on swallowing function and quality of life, as well as commonly resulting in severe dental impairment due to the loss of the bactericidal and lubricating properties of saliva.

SALIVA IN CLINICAL PRACTICE

Saliva is a readily available body fluid that can be easily collected with no adverse events, simply by getting a

patient to spit in a sample bottle. Moreover, the constituents of saliva, in particular soluble DNA or protein, have the potential to become either predictive or prognostic biomarkers. As such, a great deal of effort is ongoing in a research setting to establish the effectiveness of several putative biomarkers in clinical practice. Of the numerous examples that have been investigated to date, the presence of human papillomavirus (HPV) DNA and/or antibodies in the context of HPV-related oropharynx cancer and anti-p53 antibodies as a biomarker for oral cavity cancer outcome.[12]

Saliva has also been investigated as a medium for hormone monitoring but some limitations are evident.[13, 14] Ellison et al. have considered certain technical aspects of salivary progesterone assay and its interpretation and reviewed the utility of these assays for clinical purposes.[15] They concluded that this approach has some value because of the ease of obtaining serial samples from the same individual.[16]

SUMMARY

Salivary production and function is a complex biological process. The fine balance of salivary flow rate, volume and salivary biochemistry are all susceptible to modification altered by normal physiology, drugs, therapeutic strategies (radiotherapy and surgery) and disease states.

KEY POINTS

- Saliva, produced by salivary glands, plays an important role in oral cavity and dental health.
- There are three paired major salivary glands that collectively produce the majority of saliva: the parotid, the submandibular and sublingual glands.
- In addition, there are 600–1000 minor salivary glands present in the mucosal lining of the oral cavity and oropharynx, which also contribute to total saliva production.
- Disease and the side effects of treatment for head and neck cancer, particularly radiotherapy, alter salivary gland physiology and saliva volume and constitution.

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CHAPTER
45

IMAGING OF THE SALIVARY GLANDS

Daren Gibson and Steve Colley

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SEARCH STRATEGY

Data in this chapter may be updated by a PubMed search using the keywords: salivary, sialolithiasis and tumours.

INTRODUCTION

The ideal imaging technique would be harmless, widely available, cost efficient, highly diagnostic and reliably repeatable. It should provide excellent multiplanar capabilities and good spatial resolution, while simultaneously identifying all foci of disease involvement that require treatment near and far from the primary presentation site. Unsurprisingly, this single utopian test does not currently exist, although, across a range of modalities in usage, there is a calculated compromise to be struck with individual test strengths balanced against specific weaknesses and side effects (**Table 45.1**). Modern imaging continues to improve and can potentially act as a surrogate marker for pathological tissue diagnoses, select surgical from non-surgical candidates and also help to prognosticate. Through modern electronic radiological systems, today's surgeon is increasingly exposed to these newer diagnostic and interventional practices including guidance systems. In specific instances, image guidance can help to deliver non-surgical efficacious treatments (fluoroscopic salivary intervention, radiofrequency ablation, intra-arterial chemotherapy etc.). Functional imaging methods, such as positron emission tomography/computed tomography (PET-CT) and diffusion-weighted imaging (DWI) for neoplasia, can reflect cell turnover, metabolic consumption, vascular patterning and biological behaviour and this discipline will provide useful adjuncts to conventional anatomical images.

The current salivary gland imaging guidance for UK based clinicians is extracted from the 7th edition of the Royal College of Radiologists (RCR) Guidelines.[1] This document states that 'for salivary gland obstruction, ultrasound (US) or sialography is indicated for intermittent, food related swelling. Occlusal views are useful when US has demonstrated sialectasis but has not shown a calculus. US and/or sialography are also helpful to assess the suitability for minimally invasive management of salivary calculi.' Additionally it goes on to comment that 'for a suspected salivary mass, US is the initial investigation of choice and this can be combined with fine needle aspiration cytology when necessary. US is extremely sensitive and has a high specificity.' When the lesion extends to deeper neck spaces beyond the useful penetration of US, it suggests, 'magnetic resonance imaging (MRI) or computer tomography (CT) should be used, although, increasingly, despite the guideline recommendations, MRI and CT are being used as primary imaging modalities in clinical practice. MRI may be better than CT for malignant lesions in the assessment of local infiltration including perineural spread. Obviously, reliable staging of the thorax, if distant pulmonary metastases were suspected, would require a CT study.' The American equivalent, the similarly structured American College of Rheumatology (ACR) Appropriateness Guidance, currently offers no specific instructions for salivary imaging.

As always, any generic guidance will need to be modified around specific clinical scenarios following a focused

TABLE 45.1 Comparative imaging techniques

	Technique				
	US	**MRI**	**CE-CT**	**Conventional sialography**	**Salivary gland scintigraphy**
Advantages	• Quick examination • Widely available • No patient harm • Possible in poorly cooperative patient • Guides US-guided FNAC/ Trucut[R] • Doppler evaluates vascularity • Elastography for lesion compliance	• Excellent soft tissue contrast • Multiplanar capabilities • No radiation • Less dental artefact • Non-invasive	• Quick • Widely available • Sensitive for calculi • Broad anatomical coverage depicts • 2D and 3D reconstructions in conventional orthogonal planes	• Quick • Widely available • Excellent luminal depiction of glandular duct anatomy	• Quantification of function • Quantification of obstruction • Reproducible • Well tolerated • Easy to perform
Disadvantages	• Highly operator dependent • Non-penetrative at mandible, calculus or air interface • No depiction of deep facial spaces	• Not widely available • Relatively small field of view (cf. CT) • Long examination time (30–45 minutes) • Motion artefact • Contraindications: pacemaker, claustrophobia, non-cooperation of patient	• Radiation dose • Artefact from dental restorations and implants • Iodinated contrast issues around poor renal function and allergies	• Invasive examination (retrograde contrast injection) • Complications: bleeding, traumatic perforation, rupture duct • No information proximal to complete obstruction • Indirect information on parenchymal disease • 4–15% unsuccessful cannulation submandibular duct • Good patient cooperation required • Contraindications: acute sialadenitis, contrast allergy, thyroid disease	• Poor anatomical correlate • Radiation burden (low)

ENT examination. Any subsequent investigation will be primarily symptom-driven.

To this end, the following chapter sequentially considers:

- salivary gland obstruction and sialadenitis
- mouth dryness and glandular hypofunction
- salivary lumps and suspected neoplasms.

SALIVARY GLAND OBSTRUCTION AND SIALADENITIS

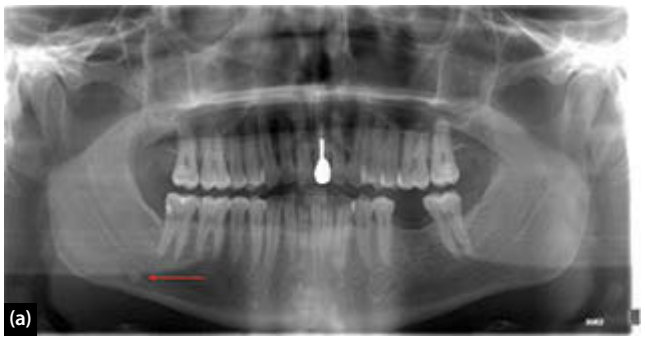
Salivary calculi (sialolithiasis), mucus plugs and ductal strictures account for the majority of cases of salivary gland obstruction. The diagnostic route for patients with obstructive symptoms may include plain radiographs (occlusal view or orthopantogram), ultrasound, conventional sialography, CT or MR imaging.

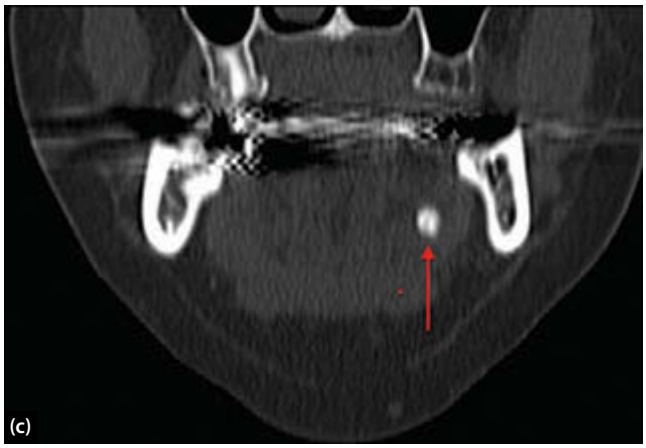
Sialolithiasis

Studies have estimated the lifetime prevalence of symptomatic salivary calculi to be 0.45%.[2] Calculus disease affects the submandibular gland far more commonly than the parotid, with sublingual and minor salivary glands being affected very rarely.

Stones may be diagnosed on plain radiographs, but ultrasound and CT are more frequently used and more sensitive in the detection of smaller calculi (**Figure 45.1**). Up to 15% of calculi are radiolucent and not visible on plain radiographs alone.

Formal sialography is still widely available but is an invasive test that carries a 4–15% failure rate, and a small risk of provoking acute sialadenitis and ostial injuries with scarring for the inexperienced operator. MR sialography is a newer non-interventional, highly T2 weighted (T2W) technique without requiring ductal cannulation or contrast





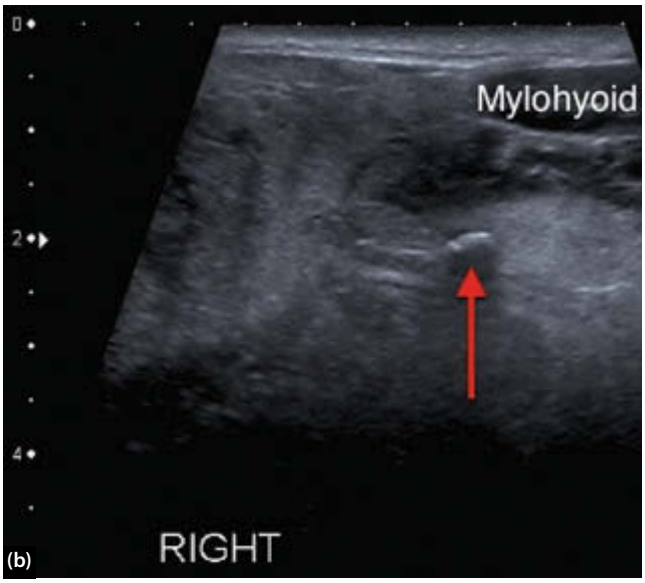
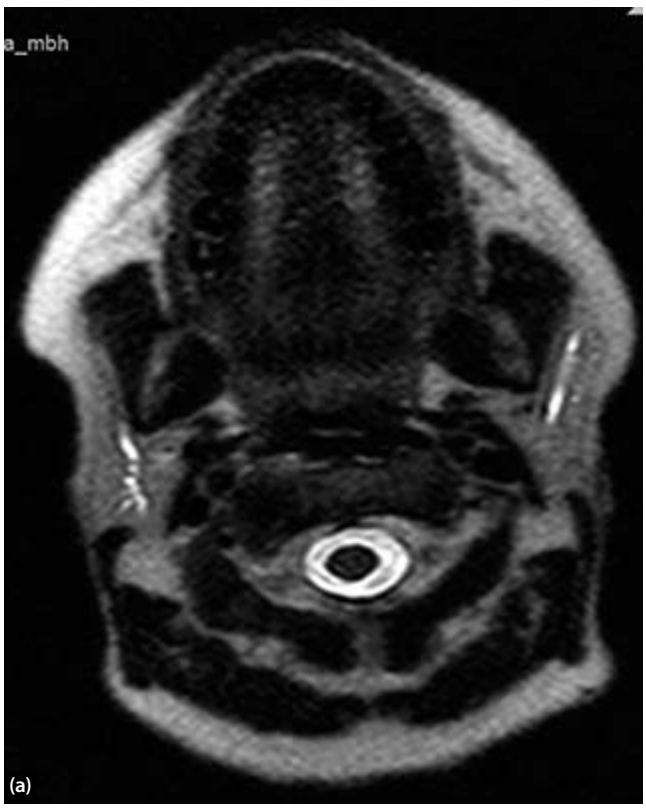


Figure 45.1 Sialolithiasis. **(a)** Orthopantogram demonstrates a right-sided SMG hiloparenchymal calculus projected over the posterior mandible; **(b)** Transverse axial ultrasound image demonstrates an echogenic hiloparenchymal calculus with acoustic shadow; **(c)** A coronally reconstructed, non-enhanced CT image demonstrates a distal left submandibular ductal calculus.



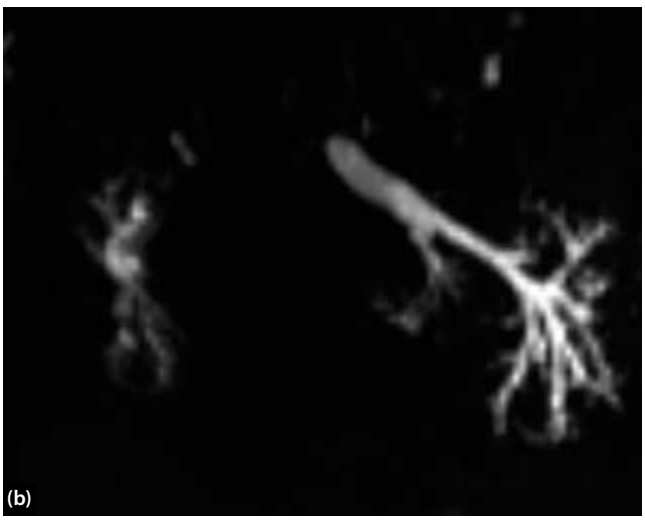


Figure 45.2 MR sialography. **(a)** Highly T2-weighted axial image to illustrate ductal fluid; **(b)** Maximum intensity projection (MIP) to highlight ductal pattern.

media as it relies upon inherent salivary fluid within the ducts to generate recordable signal (**Figure 45.2a** and **2b**). The reported sensitivity for the MR sialography diagnosis of calculous disease varies from 69% to 91%. Its specificity is 88–97%, the positive predictive value is 93–97% and the negative predictive value is 91%.[3–5]

TABLE 45.2 Advantages of CT, sialography and MRI

	Conventional sialography	Computer tomography (CT)	MR sialography
Invasive	Y	N	N
Radiation dose	+	++	N
Detects calculi	+	++	+/–
Detects mucus plugs	+	–	+/–
Detects strictures	+	–	+
Availability	+	++	+
Cost	low	moderate	high
Therapeutic options	Y	N	N

The advantages of CT, sialography and MRI are summarized in **Table 45.2**.[6]

In cooperative patients, digital subtraction techniques used at sialography will effectively remove the overprojected mandible, cervical spine and skull base, thus demonstrating the ductal opacification with iodinated contrast medium (**Figure 45.3**). In specialist centres utilizing stone retrieval devices, balloon sialoplasties and lithotripsy, a diagnostic sialogram remains a relevant and useful test. Dynamic luminal information and emptying patterns are not achievable at MR sialography. With any sialographic technique, the descriptive terminology needs to be locally agreed and standardized.

In mainland Europe, ultrasound (US) is often used as the initial diagnostic choice for obstructive symptoms and, in experienced hands, it can provide as much or more information than CT or MRI.[7] Glandular volumes and textural subtleties are easily appreciated, while the simultaneous use of a sialogogue has the potential to 'pressure test' the ductal system. The main parotid ducts are easily assessed in their entirety. However, due to the obliquity of the distal submandibular duct near the tongue frenulum, it should be remembered that US may fail to identify a small distal calculi, and complementary occlusal views are recommended.

Salivary strictures

Unlike sialolithiasis, salivary strictures preferentially affect the parotid ducts. Nearly two-thirds are a focal 'point' stricture, with the remainder being multiple beaded or long-segment, more diffuse strictures.[8] US, conventional sialography and MR sialography may all depict the site and nature of the stricture; however, due to lack of luminal detail, CT use is limited in this setting.[9]

Ultimately, identification of the type of obstruction, be it stones or strictures, is important in guiding subsequent treatment decisions. Strictures can be dilated, either under fluoroscopic control or at the time of sialoendoscopy.[10] This is generally well tolerated under local anaesthesia in an outpatient setting. With a variety of retrieval basket designs and fluoroscopic control or endoscopy, removal of calculi is a safe and effective method to treat small, mobile calculi up to 6 mm in size. Correct patient selection is vital for success. Determined by both patient factors and local expertise, larger calculi may require combined stone shattering treatments, sialoendoscopy and a transoral open approach.[11]

KEY POINTS

When presented with an obstructed submandibular gland and unilateral symptoms, care should be taken to ensure that this is due to a benign luminal phenomenon rather than extrinsic compression secondary to floor of mouth or sublingual space pathology (**Figure 45.4**).

Sialadenitis

Acute bacterial sialadenitis with sepsis is usually clinically obvious in often susceptible, dehydrated and malnourished elderly individuals. Unless there is trismus or medial tonsillar deviation to suggest deeper parapharyngeal involvement, a parotid abscess is reliably excluded with US. In the subacute setting, the role of radiology is primarily to exclude an obstructive stone, a significant treatable stricture, neighbouring nodal disease or a masquerading salivary neoplasm. More established chronic sialadenitis will eventually destroy the normal ductal architecture with sialectasia and reduce salivary flow. These persistent but low-level symptoms would still merit US evaluation, sialography and/or scintigraphy to determine whether useful gland function can be preserved as the only real surgical alternative would be excision. With these recurrent episodes, the gland becomes progressively atrophied and echo-reflective at US. With swelling and erythema in the submandibular region, odontogenic sepsis is usually excluded with an orthopantomogram (OPG).

Though multifactorial in origin and often unilateral in occurrence, a non-suppurative recurrent juvenile parotitis is a distinct entity. Emerging evidence suggests that early sialoendoscopy and/or therapeutic interventional sialography may avoid glandular destruction, symptom deterioration and the eventual need for gland excision.[12] Punctate sialectasis follows repeated infections and this clouds the initial precipitating aetiological cause. A US examination is contributory to patient workup and often

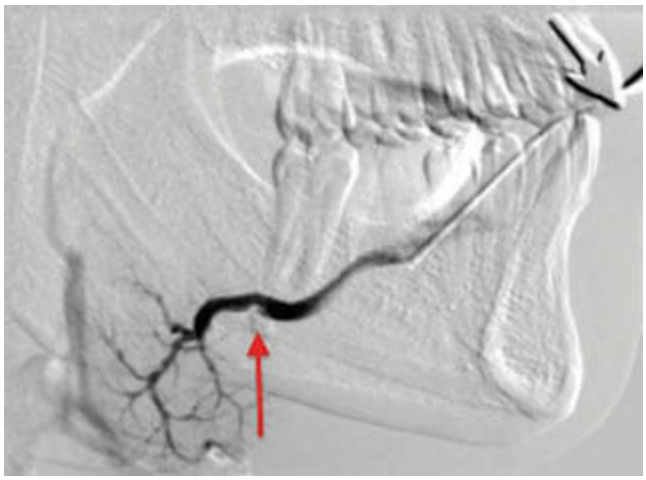


Figure 45.3 Digital subtraction sialography illustrates a right-sided, partially obstructing luminal calculus.

demonstrates a bulky, hyperaemic gland. The ducts may be irrigated with antibiotic and steroid solution at the time of intervention.

Rarer still, TB, actinomycosis, cat-scratch disease, brucellosis and toxoplasmosis can all precipitate acute episodes of sialadenits.

DRY MOUTH AND GLANDULAR HYPOFUNCTION

The clinical presentation of a non-obstructive, non-suppurative multisite glandular swelling or even a unilateral asymmetric, atypical finding may be secondary to a diffuse inflammatory or systemic condition. Although US remains the first imaging modality of choice, it has a limited range of anatomical coverage and the radiologist will need to appreciate that non-mealtime, bilateral salivary

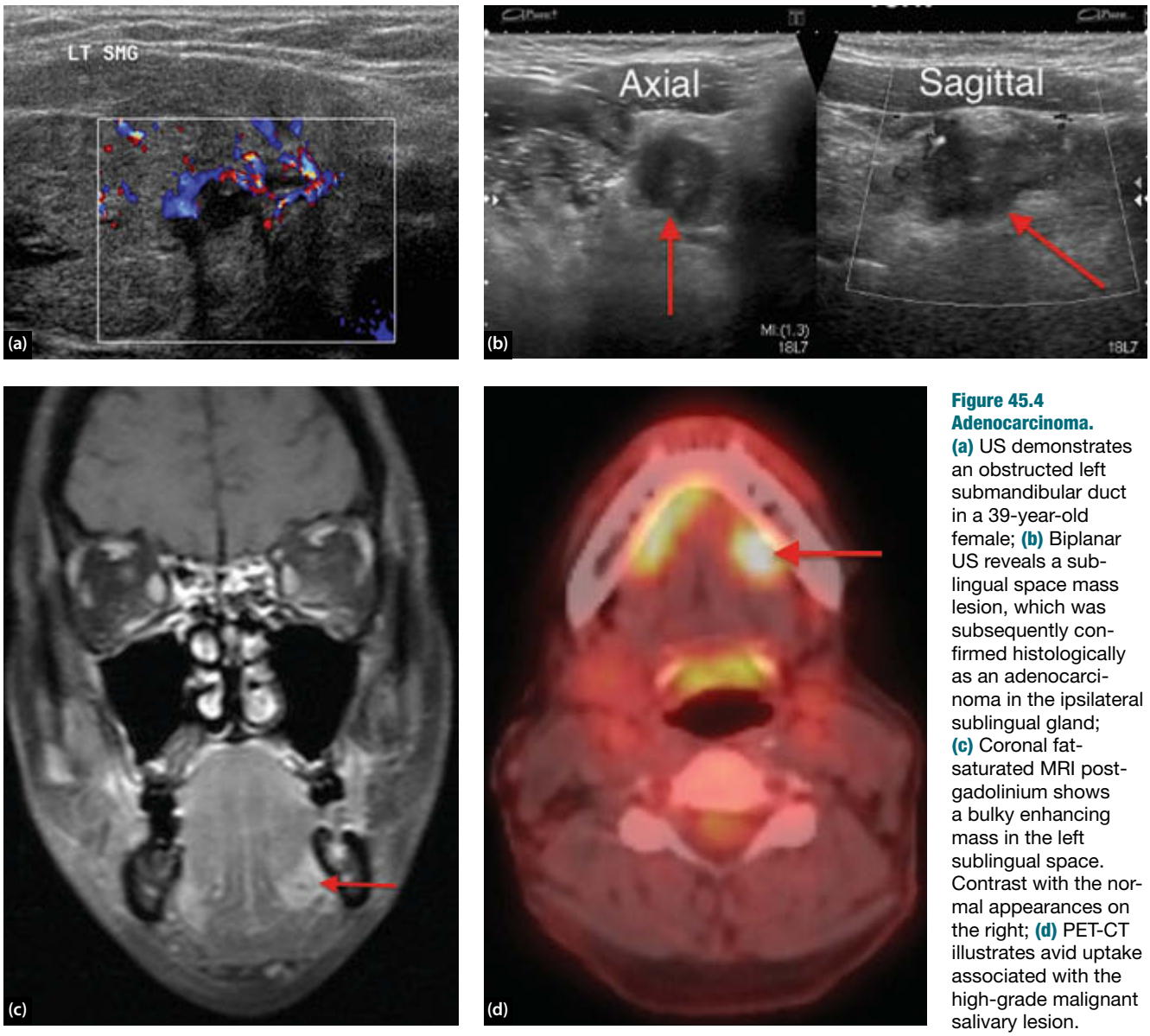


Figure 45.4 Adenocarcinoma. **(a)** US demonstrates an obstructed left submandibular duct in a 39-year-old female; **(b)** Biplanar US reveals a sublingual space mass lesion, which was subsequently confirmed histologically as an adenocarcinoma in the ipsilateral sublingual gland; **(c)** Coronal fat-saturated MRI post-gadolinium shows a bulky enhancing mass in the left sublingual space. Contrast with the normal appearances on the right; **(d)** PET-CT illustrates avid uptake associated with the high-grade malignant salivary lesion.

symptoms with or without constitutional features raises a wider possibility of a more nebulous, potentially multifocal underlying condition.

Sjögren's syndrome

Initially presenting with intermittent swelling of the major salivary glands, primary Sjögren's disease is an autoimmune disorder that will chronically destroy salivary and lacrimal exocrine glands to result in xerostomia and xerophthalmia. With a coexistent systemic arthropathy, such as rheumatoid arthritis, it is termed secondary Sjögren's syndrome. Accelerated dental decay may be seen on an OPG (**Figure 45.5a**). As part of the patient workup, the 2002 American-European Consensus Report revised criteria for the secure diagnosis of Sjögren's disorder includes abnormal sialographic and/or scintigraphy studies with delayed uptake, reduced concentration and/or delayed secretion of tracer material.[13, 14] Scintigraphy involves intravenous injection of approximately 80–100 megabequerels of pertechnetate (^{99}Tc) in an attempt to quantify glandular secretory dysfunction. This tracer is preferentially taken up and secreted via the duct epithelium and counts are acquired over a 30–45-minute period using gamma camera detectors. As a two-phase study, a sialogogue is given midway through the test to define a secretory phase and quantitative time-activity curves are routinely generated. Antibody screening including titration of rheumatoid and anti-nuclear factors as well as anti-Ro (SS-A) and anti-La (SS-B) antibodies may help alongside radiological studies but, ultimately, a labial mucosal biopsy is the most specific diagnostic test.

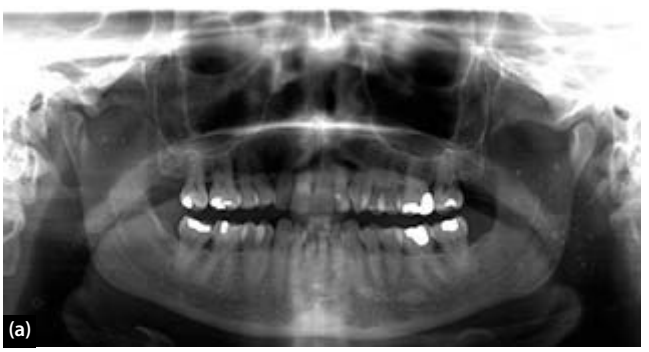
There are now ample studies documenting the role of US in the non-invasive diagnosis of Sjögren's.

The ultrasonic features described with Sjögren's disease will vary with the stage of presentation with initial hypoechoic, pseudocystic regions and hyperaemia. These 'cysts' may pathologically reflect numerous repeated ductal obstructions due to lymphocytic infiltration and intraparotid nodal hyperplasia.

Chronically, gland volumes are markedly reduced with eventual fatty replacement. Standard fluoroscopic sialography and MRI sialography have been used to evaluate characteristics ductal patterns in affected and the long-established grading system initially proposed by Rubin and Holt[15] is still approximated for both techniques. Larger areas of cavitation, benign lymphoepithelial lesions (BLEL) and parenchymal atrophy will result in globular areas of ductal sialectasia and beading, although, these are not pathognomic features that can also be seen with straightforward chronic sialadenitis. More recently, with MR DW techniques, researchers have attempted to differentiate normal glands from those affected by inflammatory, connective tissue diseases.[16] In longstanding cases, CT will elegantly demonstrate multiple bilateral punctate calcific foci with atrophy (**Figure 45.5b**).

Chronically, with elevated risks of developing marginal zone B-cell lymphomas within parotid or submandibular gland tissue, urgent cross-sectional imaging +/– biopsy is required for an enlarging, painless parotid mass. Currently, no evidence supports interval imaging for surveillance.

With considerations of a wider differential, those having undergone previous head and neck radiotherapy, with occult HIV and adenopathy, with hepatitis C viral infections, occult sarcoidosis or complicating graft-versus-host disease, can all present with similar symptoms and some of these entities will need a high index of clinical suspicion in high-risk individuals.



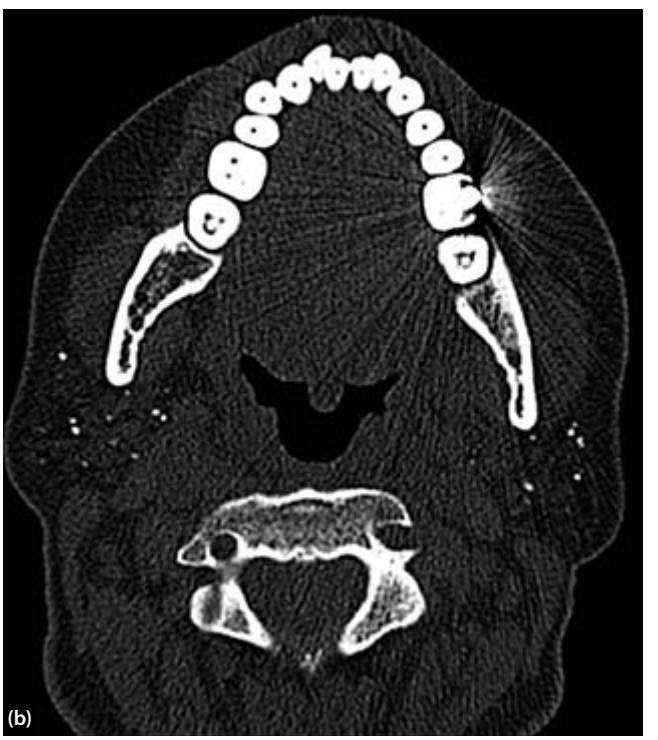


Figure 45.5 Sjögren's syndrome. **(a)** OPG shows multiple small calcific densities projected over both parotid glands; **(b)** Non-enhanced axial CT shows multiple tiny glandular calculi.

Sarcoidosis

With otolaryngological manifestations in around 10% of patients, cervical adenopathy, parotid or submandibular swellings and cranial nerve palsies are the commonest head and neck presentations of this multisystem disorder. Diffuse, intermittent parotid gland enlargement is usually bilateral but, when asymmetric, an ultrasound guided fine-needle aspiration cytology (USg FNAC) can be useful.[17] Notably, conventional sialography is often normal in the presence of florid systemic features whilst biopsy of the affected tissue or nodal excision is usually diagnostic. Eventually, the normal tissue will be replaced by fat infiltration that can have striking appearances on fat sensitive T1W sequences. A brain and skull base MRI with post contrast images is indicated in the presence of cranial neuropathies or meningism. Radiolabelled gallium scans with associated mediastinal and hilar adenopathy can yield a typical 'lambda' or 'panda' sign, which are not entirely specific radiologic findings.

IgG4-related systemic disease

This emerging and obscure condition was first reported in 2003.[18] It has numerous head and neck manifestations that now encompass both Mikulicz syndrome and Kuttner's pseudotumour with initially enlarged lacrimal and submandibular glands. Affected patients can present with a tentative diagnosis of lymphoma or malignancy due to weight loss and adenopathy. A detailed, relevant clinical history may identify prior multi-organ involvement that may include acute pancreatitis and previous renal failure. The eventual, often delayed but highly treatable diagnosis is securely made on the basis of raised serum IgG4 concentrations. CT or MRI imaging demonstrates bilateral cervical adenopathy, glandular swelling and excessive enhancement of salivary and lacrimal tissue in the context of mild SICCA symptoms (**Figure 45.6a, b, e**).

A typical geographic textural abnormality and hypervascularity is seen on US Doppler imaging (**Figure 45.6c, d**). A FNAC or biopsy is often performed to distinguish this highly steroid responsive protean disorder from a parenchymal mass lesion or a lymphoproliferative disorder. More recently, PET-CT has been proposed to stage and monitor aggressive, multi-focal disease.[19]

It is currently a matter of debate as to whether there is an increased propensity for affected individuals to develop complicating lymphomas. Critically, an early diagnosis and immunosuppressant therapy invariably leads to a dramatic clinical improvement and avoidance of life threatening abdominal, renal and vascular complications.

Radiotherapy

Radiotherapy for head and neck cancers can often induce debilitating xerostomia in a dose-predictable fashion. Other than subjective patient reporting of symptoms and salivary flow studies, conventional sialography and/or scintigraphy are the most commonly utilized tests for further documentation of impaired glandular function and stricture formation.

Follow-up CT studies will initially show avid enhancement and global increased density and, over months, this is followed by irreversible dose-dependant reduction in gland volume with ductal ectasia and fibrosis (**Figure 45.7 a–d**). MR sialography may show a correlation between submandibular gland dysfunction and xerostomia.[20] Parotid doses over 60 Gy inevitably lead to irreversible xerostomia, while mean doses below 24 Gy will usually preserve salivary flow. At MRI, Nomayr et al.[21] documented preferentially larger volume losses during treatment in the parotid tissue rather than the submandibular glands. The parenchymal volumes will alter significantly during treatment when compared with baseline imaging.[22]

US studies[23] describe parenchymal heterogeneity, increased duct conspicuity and lowered vascular resistive indices in previously irradiated glands, and these findings are believed to relate to acute inflammatory infiltrates maturing with resultant chronic fibrosis. With the advent of intensity-modulated radiation therapy (IMRT) techniques, reduced dose delivery can be achieved for selected organs at risk. The prospective, randomized PARSPORT trial confirmed that parotid-sparing IMRT plans improved subjective symptoms,[24] salivary flow rates and scintigraphy results. Where IMRT planning is used, it is now the standard of care to use parotid-sparing planning techniques.

SALIVARY MASSES AND SUSPECTED NEOPLASMS

The 2005 World Health Organisation[25] pathological classification for salivary gland tumour subtypes is generally viewed as complex and the evidence-based data around the ideal management of these rare lesions is relatively poor.

Therefore, local, national and international experiential variations in surgical and radiological practice will exist. Workup may involve all or some of the following: US; USgFNAC; core biopsy; CT staging; MRI; frozen section; and/or surgical excision. Obviously, different sampling techniques will provide variable amounts of histopathological tissue with which to secure a reliable pre- or post-operative diagnosis. Excision of the salivary mass as per local protocols ultimately yields the definitive diagnosis. At added expense, functional imaging tests may go on to provide non-invasive methods of tumour characterization with promising initial results.[26]

Ultrasound (US) and ultrasound-guided fine-needle aspiration cytology (USgFNAC)

Ultrasound is the preferred initial test for palpable salivary gland masses. It is tolerated well, cheap, quick

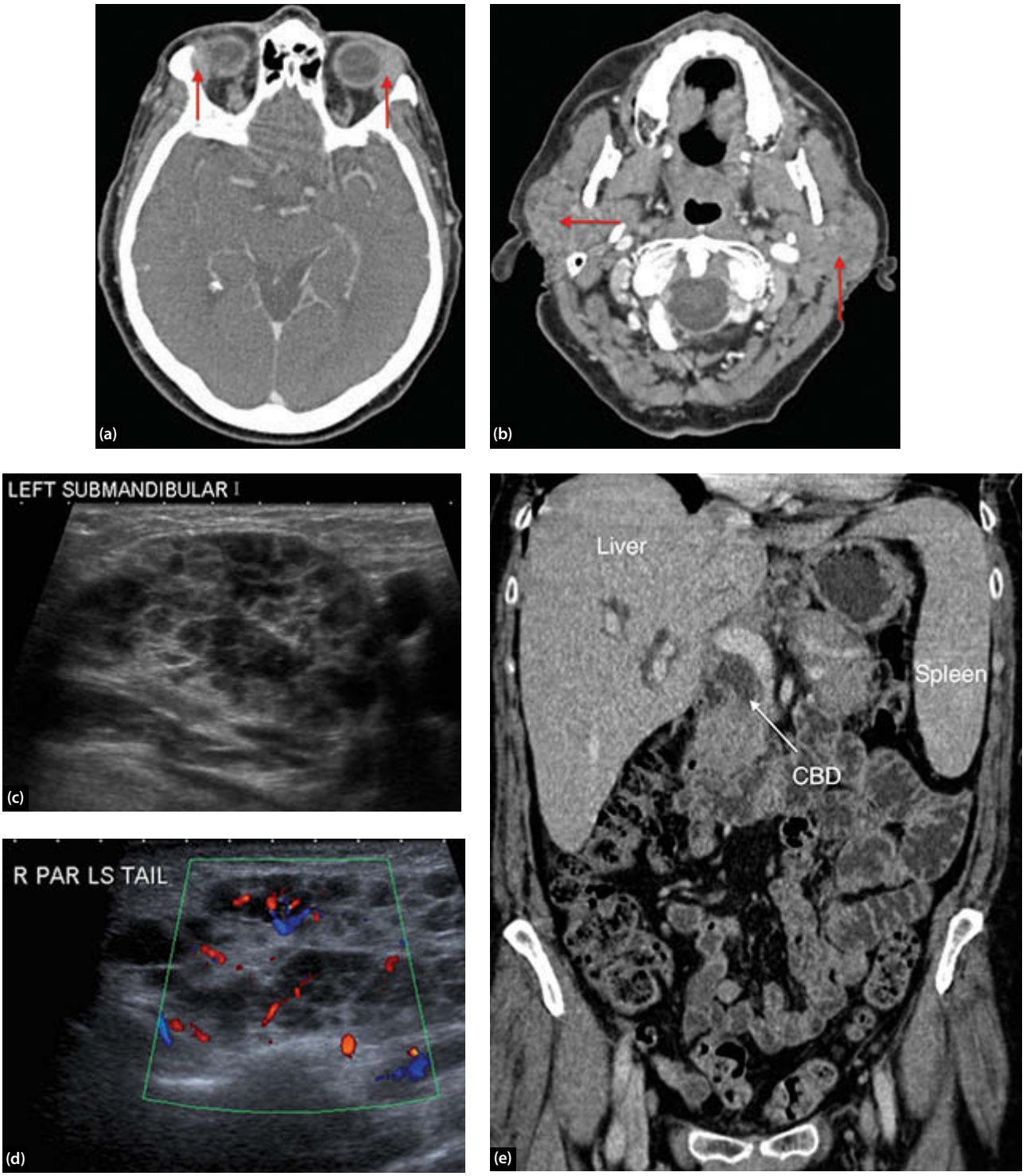
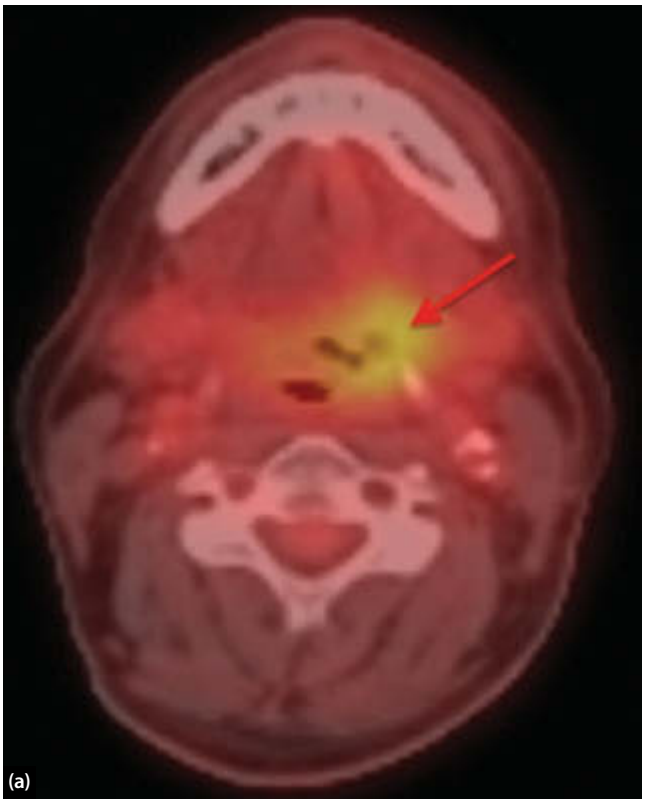
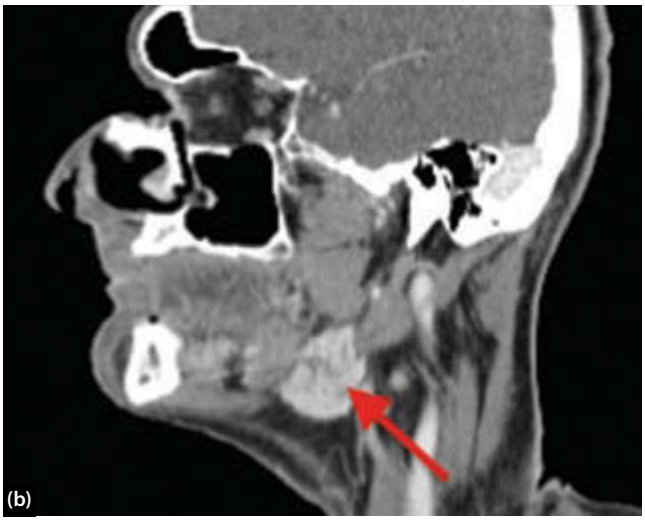


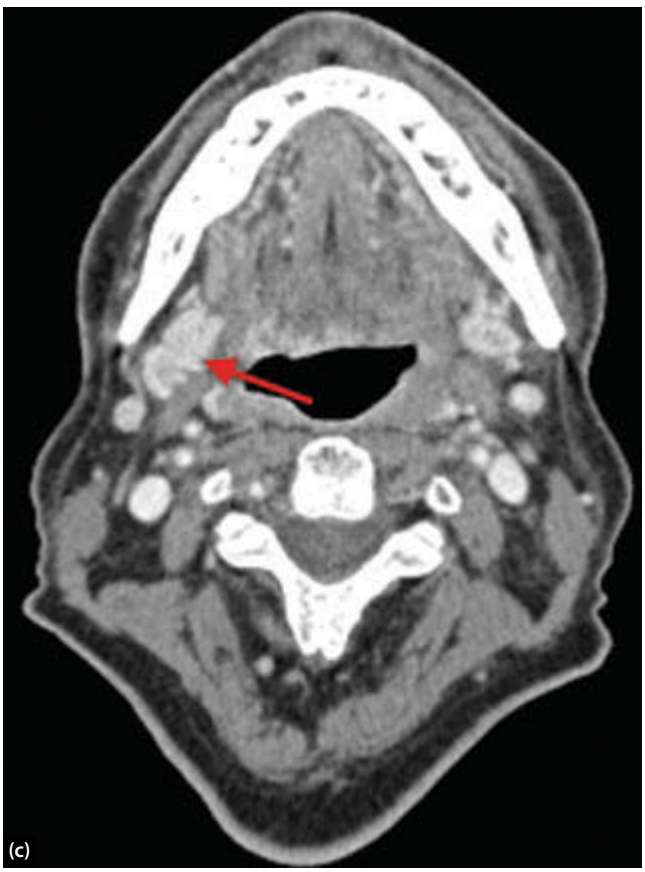
Figure 45.6 IgG4related systemic disease. **(a)** Enlarged, bilateral lacrimal glands; **(b)** Symmetric bilateral parotid gland enlargement; **(c)** Bilateral heterogeneous glands with hypoechoic regions; **(d)** Hyperaemic glandular parenchyma; **(e)** Contrast CT (coronal) shows pancreatitis and hepatosplenomegaly with an obstructed CBD.

and accessible. It allows image guided biopsies and assessment of coexistent pathologies and cervical nodes. It is, however, operator-dependent. Normal variants such as gland ptosis in the elderly and congenital anatomical mylohyoid defects are readily appreciated.

A reliable pre-operative diagnosis facilitates better informed consent, potential conservative management of benign tumours in the frail, and streamlined operative list management. Radical surgical approaches will only be undertaken in the presence of a confirmed malignancy. The drawbacks of freehand FNAC are well-documented[27] and, where feasible, core biopsy should be performed for a definitive histological diagnosis prior to intervention.







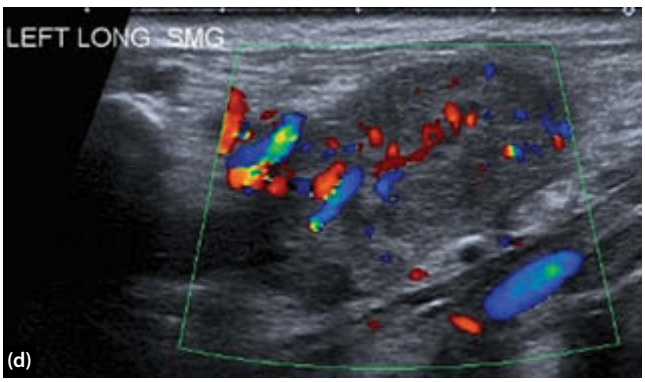


Figure 45.7 Salivary gland changes after radiotherapy. **(a)** PET-CT demonstrates left base of tongue tumour; **(b)** Enhanced CT (sagittal) shows avidly enhancing SMG; **(c)** Enhanced CT (axial) shows avidly enhancing SMG; **(d)** US demonstrates hypoechoic, hypervascular gland.

In 2010, Sriskandan et al.[28] published retrospective data on the accuracy of US alone in discerning benign from malignant lesions for 220 referred parotid lumps. The sensitivity, specificity and diagnostic accuracy for malignancy was 91%, 93% and 93% respectively, with nine false positives and four false negative cases. The majority of pleomorphic adenomas had classic 'benign' appearances; being lobulated, clearly defined, relatively echo-poor and homogenous, however, posterior acoustic enhancement and vascular patterning on Doppler imaging seemed relatively poor discriminators.

Cystic, septated and bilateral disease often correctly suggested benign Warthin's tumours.

As a non-invasive imaging adjunct, sonoelastography uses graduated compressions to assess tissue stiffness. Dumitriu et al.[29] assessed lesional compliance in 74 benign and malignant salivary gland tumours with a histological end point. However, elastography has failed to consistently show significant differences between benign and malignant lesions and is currently unable to eliminate FNA or biopsy from the diagnostic work-up.

USgFNAC without local anaesthetic infiltration is a rapid and safe outpatient procedure with no absolute and a few relative contraindications. Consent will require a discussion of infrequent infective complications, tumour

seeding and haemorrhagic risk. In 1997, the Papanicolaou society[30] published guidelines that estimated that the risk of seeding with small needles (<22 G) was between 0.003% and 0.009%. Standardized cytological categories are: (i) inadequate; (ii) benign; (iii) atypical cells present; (iv) suspicious for malignancy; or (v) overtly malignant.[31] Perhaps unsurprisingly, using pathological correlates, data has consistently shown that the diagnostic accuracy of USgFNAC is most dependent upon the site of aspiration, the number of needle passes, the number of prepared slides submitted and the experience of the individual performing and interpreting the FNAC. It is made more accurate when the individual interpreting the FNAC is the same individual who obtains the aspirate material.[32] It is routinely performed with a 23- or 25-gauge, long bevel needle with a capillary technique as proposed by Zajdela et al.[33] Advantageously, US guidance will avoid hypocellular, necrotic or cystic regions that pose diagnostic challenges. Both air-dried and alcohol-fixed slides are prepared bedside. Flow cytometry and immune-phenotyping techniques or trucut core biopsies will be required if lymphoma is suspected and surgical excision is to be avoided.

Articles concerning USgFNAC yields[34–37] have reported sensitivities ranging from 62% to 98% and specificity ranges from 94% to 100%. For 191 salivary tumours, Howlett et al.[38] conducted a 1-year audit within a rapid-access clinic setting and found a diagnostic sensitivity of 64% and specificity of 100%. Zhang et al. in 2009[39] published data showing that overall accuracy in distinguishing benign from malignant lesions was 79.1% and the sensitivity for salivary neoplasia was 89.4%. In 2011, a retrospective study[40] looked at USgFNAC for 245 parotid and submandibular salivary aspirates without immediate adequacy assessments. A cytological diagnosis was possible in 215 aspirates (87.8%). The sensitivity, specificity and diagnostic accuracy of the test in separating benign from malignant lesions were 75.7%, 100% and 95.8% respectively. In the recent pathology literature, it seems clear that the ideal FNAC is immediately prepared by skilled technicians trained in slide preparation with further on-site 'live' technical expertise available for prompt adequacy assessments; however, this model has significant increased service cost implications. With this model in place, the group quotes an overall accuracy rate for salivary FNAC of between 90% and 95%. The UK National Institute for Health and Care Excellence (NICE) guidelines recommend having a cytopathologist or biomedical scientist to assess the cytology sample adequacy when the procedure is carried out.

In 2007, Howlett et al.[41] considered the additional merits of avoiding surgery for Warthin's tumours in elderly, frail individuals using US-guided core biopsies for 135 superficial parotid lesions. With this same technique, low-grade lymphoma is reliably separated from nodal hyperplasia. The group comments that seeding has only been documented with bigger gauge needles in older studies but, undoubtedly compared with FNAC, there will be an increased risk of haematoma formation and facial nerve injuries.

Benign neoplasms

PLEOMORPHIC ADENOMAS

Given that 90% of parotid pleomorphic adenomas occur within its superficial lobe, these are readily assessed and sampled at USgFNAC (**Figure 45.8a**). Submandibular gland masses and palpable minor salivary gland lesions are also easily sampled. With typical image findings, some authors have proposed that US alone is sufficient prior to surgery.[42] A radiologist's confidence for facilitating a

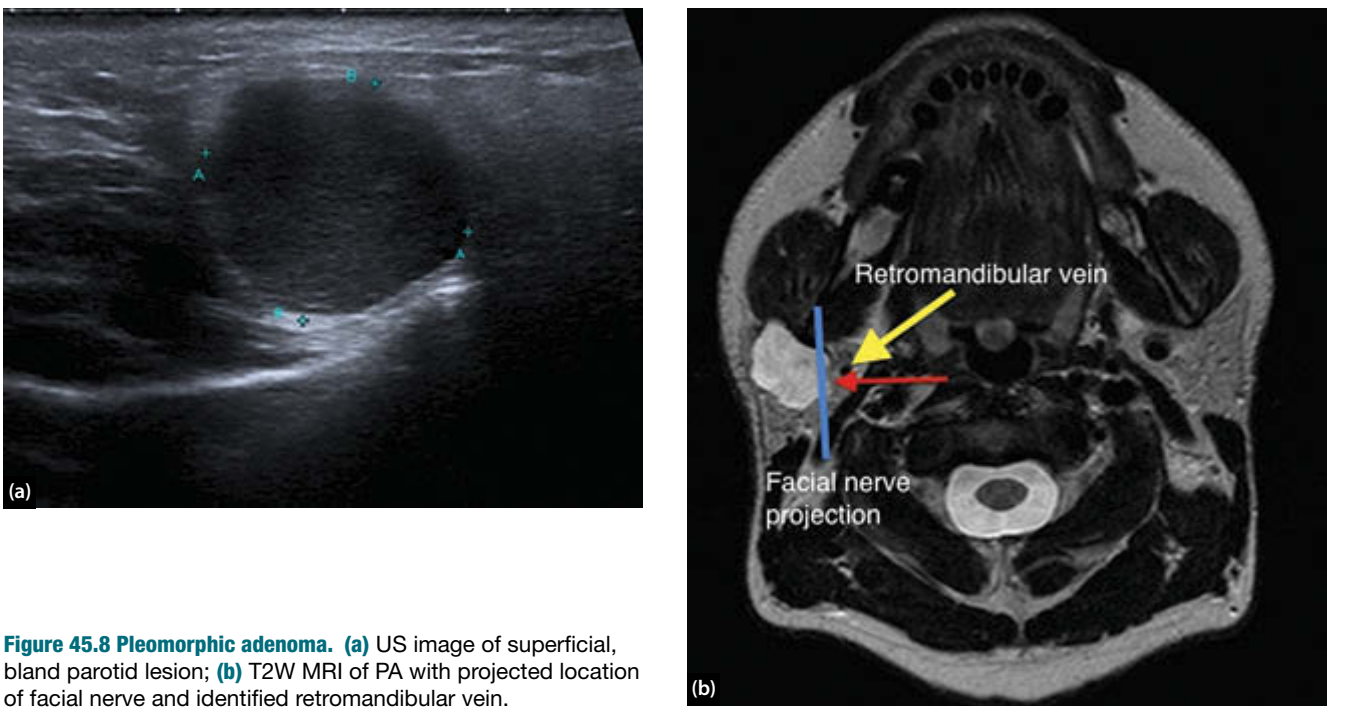


Figure 45.8 Pleomorphic adenoma. (a) US image of superficial, bland parotid lesion; **(b)** T2W MRI of PA with projected location of facial nerve and identified retromandibular vein.

successful superficial parotidectomy or extracapsular dissection is dependent upon the expected position of the facial nerve branches lying lateral to the often-identified retromandibular vein. A commonly used surrogate MR technique to plot the expected facial nerve trajectory from the stylomastoid foramen is described by Ariyoshi et al.[43] using the digastric muscle and the mandibular ramus (**Figure 45.8b**).

Newer T1-like gradient echo sequences (FISP/GRASS and magnetization-prepared rapid acquisition gradient echo sequences) and double echo steady state/reversed FISP sequences have had recent success in actually demonstrating the intraparotid facial nerve.[44, 45]

MRI, with its excellent soft tissue definition and lack of ionizing radiation, is routinely indicated for the rarer deep lobe lesions (**Figure 45.9c** and **d**), ill defined or

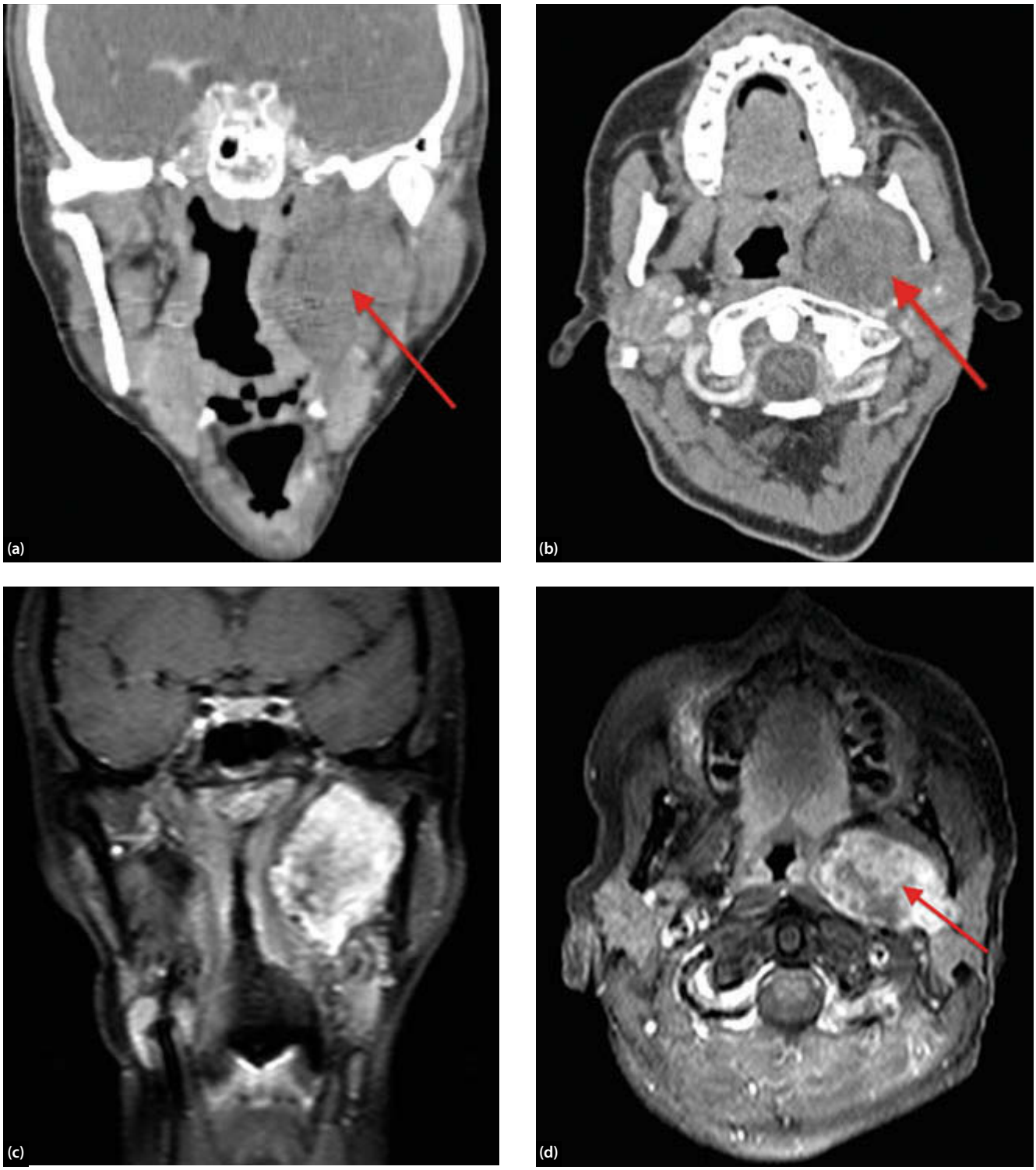


Figure 45.9 **(a, b)** Contrast-enhanced CT images of deep lobe PA; **(c, d)** Post-gadolinium, fat-saturated MR images of deep lobe PA.

infiltrative masses, in the context of facial nerve symptoms or suspected perineural disease and when FNA is suggestive of malignancy. Axial or coronal T2W sequences, fat-saturated contrast-enhanced and DWI are commonly performed. At MRI, pleomorphic adenomas typically follow the signal characteristics of fluid, appearing homogenously low signal at T1W imaging and 'T2 fluid bright'. They demonstrate variable moderate and sometimes delayed enhancement patterns following gadolinium. The thin surrounding capsule and pseudopodia formation of the commonest myxoid/ hypocellular pleomorphic subtype with a relatively higher propensity for recurrence is not visualized at imaging.[46] The less prevalent hypercellular variant is more likely to demonstrate atypical low signal intensity (SI) on T2W images. If a pleomorphic adenoma is managed non-operatively, the risk of malignant transformation is reported to increase with chronicity and this is suggested at MRI with T2W hypointensity (hypercellularity), rapid interval growth, abnormal facial nerve enhancement and ill-defined infiltrative margins. In small case series, DWI shows promising follow-up results.[47]

The literature suggests pleomorphic adenoma recurrence rates of around 1–4% after treatment and these usually occur in the first decade after surgery. In the larger series, two-thirds of recurrent disease is multifocal and the majority should maintain the same benign imaging characteristics of the initial tumour. Recurrent, small subcutaneous nodules are frequently seen and disease can present in a remote site from the operative bed.[48] Routine post-operative surveillance imaging is a costly and contentious issue.

WARTHIN'S TUMOUR

Warthin's tumour is the second most frequent parotid gland tumour with a 10–15% incidence of bilaterality. US highlights a well-defined, somewhat heterogenous, hypoechoic lesion that may be septated and partially cystic. Subacute haemorrhage or proteinaceous material will yield 'T1 bright signal' at MRI and possibly a hypointense signal rim indicative of chronic haemosiderin and blood degradation products. Enhancement is classically poor apart from the vascularized septations and the lesion may have restricted signal on DWI (**Figure 45.10**). A confident pre-operative diagnosis in those with significant comorbidities may avoid surgery altogether.

ONCOCYTOMAS

Oncocytomas most commonly present as solitary lesions in the parotid glands and these rare tumours are difficult to distinguish from benign and low-grade salivary tumours on routine US and MR imaging alone. A case series of nine patients describes a 'vanishing mass' with hypointense and isointense signals on T1 and fat-saturated T2W sequences respectively in eight of the pathologically confirmed lesions.[49] Like Warthin's tumours, these will demonstrate cystic degeneration and have a propensity to bilateral disease (10%).

Malignant neoplasms

The NICE guidelines on improving head and neck cancer outcomes in 2004[50] promoted appropriately set-up and funded fast track 'one-stop' clinical and US assessment clinics to provide same-day tissue biopsies and prompt diagnoses. The most common malignant salivary tumours are mucoepidermoid, adenoid cystic, acinic cell, adeno- and squamous carcinomas. Approximately 20% of all parotid tumours, half of the submandibular gland tumours and more than 90% of sublingual tumours are malignant. Malignant tumours can deceptively show the same imaging characteristics as their benign counterparts.

KEY POINTS

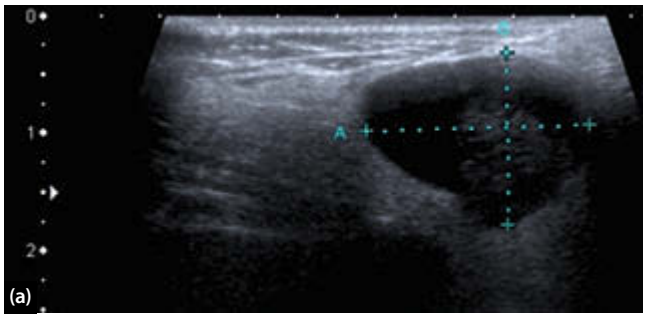
- Common knowledge states that there is an inverse relationship between the volume of the salivary gland and the risk of malignancy.
- It should be remembered that minor salivary glands are present throughout the upper aerodigestive tract including the sinonasal cavity and trachea.
- Intermediate grade and aggressive tumours with metastatic potential are disproportionally more frequent in the sublingual and minor salivary glands.

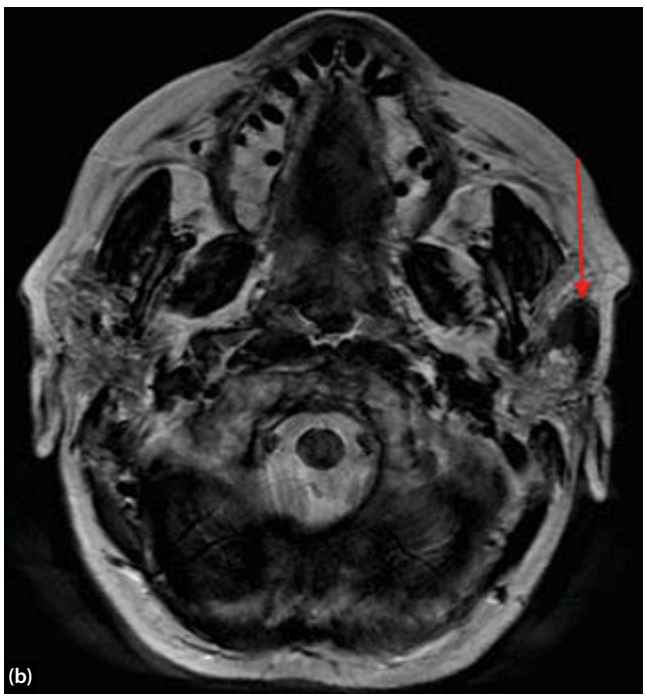
A firm, fixed, painful lesion with rapid growth or possible cranial nerve deficits and local adenopathy strongly suggests malignant characteristics. Image interpretation is primarily focused towards these adverse prognostic indicators.[51] Imaging features more suggestive of malignancy are lesional inhomogeneity, posterior acoustic shadowing and raised inherent vascular flow at US. With a good positive predictive value, ill defined and infiltrative margins imply malignancy. The absence of T2W bright fluid signal with avid enhancement patterns at MRI renders a focal lesion as indeterminate, possibly malignant and this will require prompt surgical excision. MR signal characteristics and tumour grades are poorly correlated. Perineural facial or trigeminal nerve enhancement (best depicted on fat-saturated, post-gadolinium images), obscuration of fat around widened skull base neural foramina, biopsy proven cervical lymph node metastasis, remote lung nodules and destructive bone lesions are highly sensitive indicators of loco-regional and distant metastatic disease.

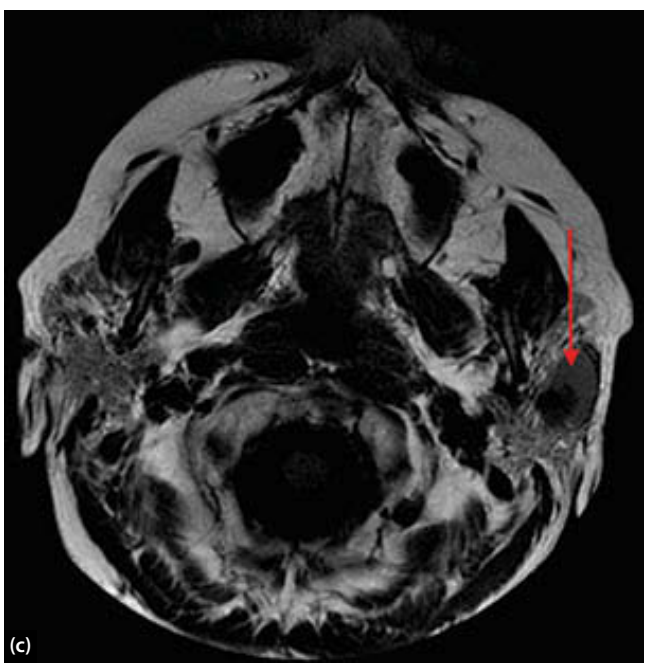
Contrast-enhanced CT is universally used to stage presenting aerodigestive squamous cell carcinomas and it is sensitive in detecting pulmonary metastasis that would generally preclude curative surgery in high-grade salivary malignancies. However, its routine use in evaluating the salivary gland parenchyma is limited due to poor soft tissue characterization. Moreover, salivary gland lesions may be concealed amongst dental amalgam artefact and the surrounding normal avid enhancing gland parenchyma. A skull base and neck CT study would be complementary to MRI when associated bony erosion is suspected.

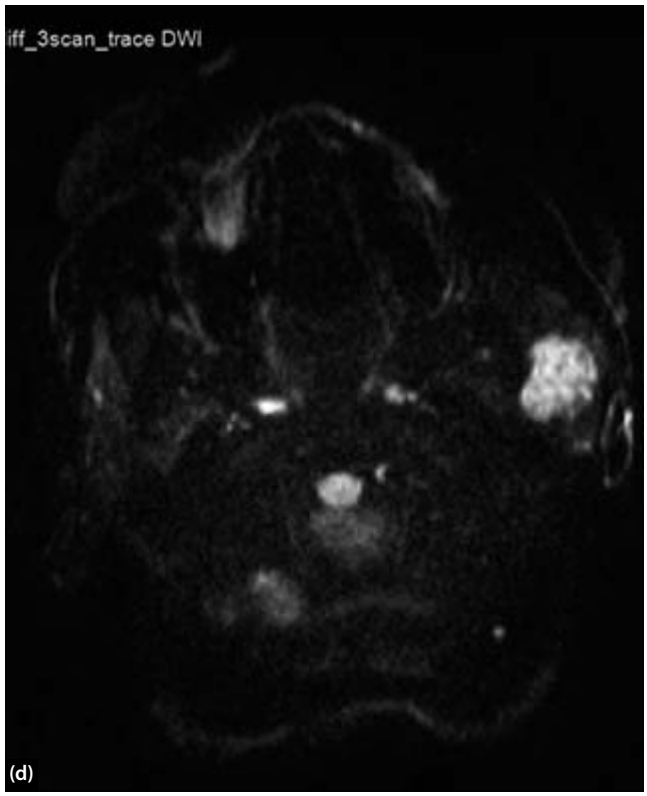
MUCOEPIDERMOID TUMOURS

Mucoepidermoid tumours are the most common parotid malignancy, and constitute 12–29% of all salivary









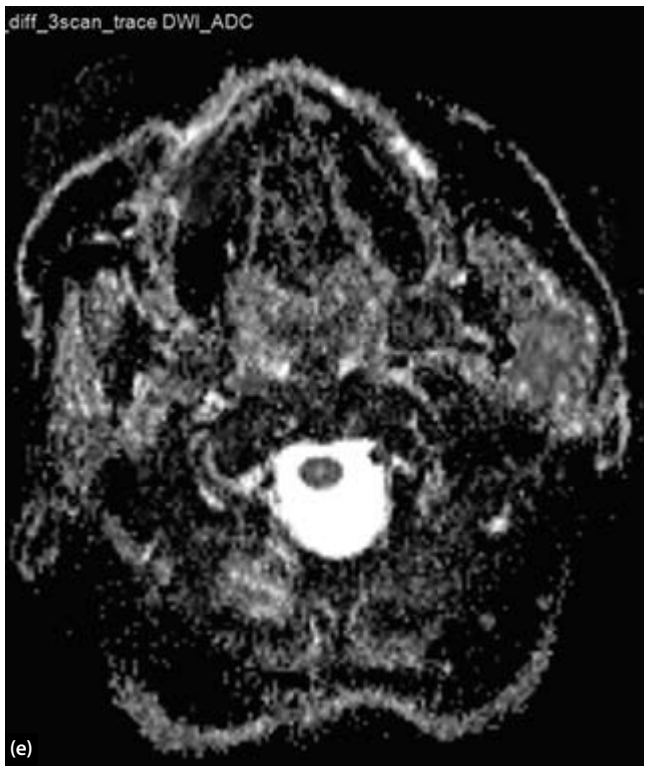


Figure 45.10 Warthin's tumour. **(a)** Axial US of well-circumscribed, heterogenous superficial Warthin's lesion; **(b)** Axial T2W MR of left parotid gland Warthin's tumour; **(c, d)** Diffusion-weighted imaging of a Warthin's tumour; **(e)** matched ADC image demonstrating hypercellularity.

malignancies. Classified into high-, intermediate- or low-grade tumours, they may have abundant fibrous tissue that is hypointense across MR sequences. Cystic change may be present.

ADENOID CYSTIC CARCINOMAS

Adenoid cystic carcinomas are overall the second most common salivary gland lesion but the commonest malignant tumour within the submandibular glands. Cribriform, tubular and solid subtypes exist and cellularity correlates with prognosis. Hypercellular areas tend to yield hypointense signal on T2W sequences and are more common with the solid subtypes.[52] Local perineural spread should be always be sought pre-operatively on contrast-enhanced MR images. Larger tumours may have intralesional bleeds with bright signal foci on T1W imaging.

INTRAPAROTID NODAL METASTASIS: LYMPHOMA, SCC AND MELANOMA

As a drainage pathway to the face, lateral scalp and external auditory canal, occult skin squamous cell carcinoma (SCC) and melanomas may present as parotid masses (**Figure 45.11**). Primary salivary gland lymphomas are more common in immunosuppressed individuals and those with background chronic autoimmune disease such as pre-existent Sjögren's disease. The imaging findings and long clinical histories are suggestive clues. At US, bulky, non-necrotic hypoechoic large intra-parenchymal nodes with distorted hila are also highly suggestive of secondary lymphoma, which will require staged abdominopelvic imaging.

Newer functional techniques

Whilst the overwhelming success of DWI in ENT has been for the evaluation and follow-up of cholesteatomatous ear disease, it has also been studied to differentiate salivary gland tumours. Its spatial resolution is poor but it is always acquired rapidly alongside conventional anatomical imaging. Transient magnetic gradients reflect local intra- and extracellular water diffusion amongst macromolecules, endothelium, cell membranes and hypercellular environments that can characterize pathological tissues in more detail. Quantitative values (apparent diffusion coefficients or ADC values) are obtained routinely and these can be prospectively correlated with subsequent histopathological findings. To dichotomize and oversimplify, high ADC values imply a benign phenotype, while reduced values suggest a greater chance of malignancy. Fluid and vascular flow can confound the validity of results[53] and the different ratios of serous and mucinous salivary glands yield differing ADC values in healthy individuals.[54]

Perhaps less favourable than initial reports, Habermann et al.[55] prospectively considered 136 consecutive parotid tumours and they were significantly and successfully able to separate pleomorphic adenomas and myoepithelial adenomas from other cell types. Despite variation in their biological behaviours, Warthin's tumours, mucoepidermoid, acinic cell and basal cell adenocarcinomas (surgical candidates) were poorly separated with overlapping, somewhat indeterminate results.

The significant histological heterogeneity in salivary neoplasms and small study sizes do not favour the development of these newer techniques. Sumi et al.[56] used intravoxel incoherent motion (IVIM) MR sequences to prospectively study 31 salivary gland tumours with histological correlation and derived parameters that could be successfully used to partition malignant and benign entities. Conceptually, it is thought that densely packed, small malignant cells, with high nuclear : cytoplasmic ratios tend to have poor associated diffusivity.

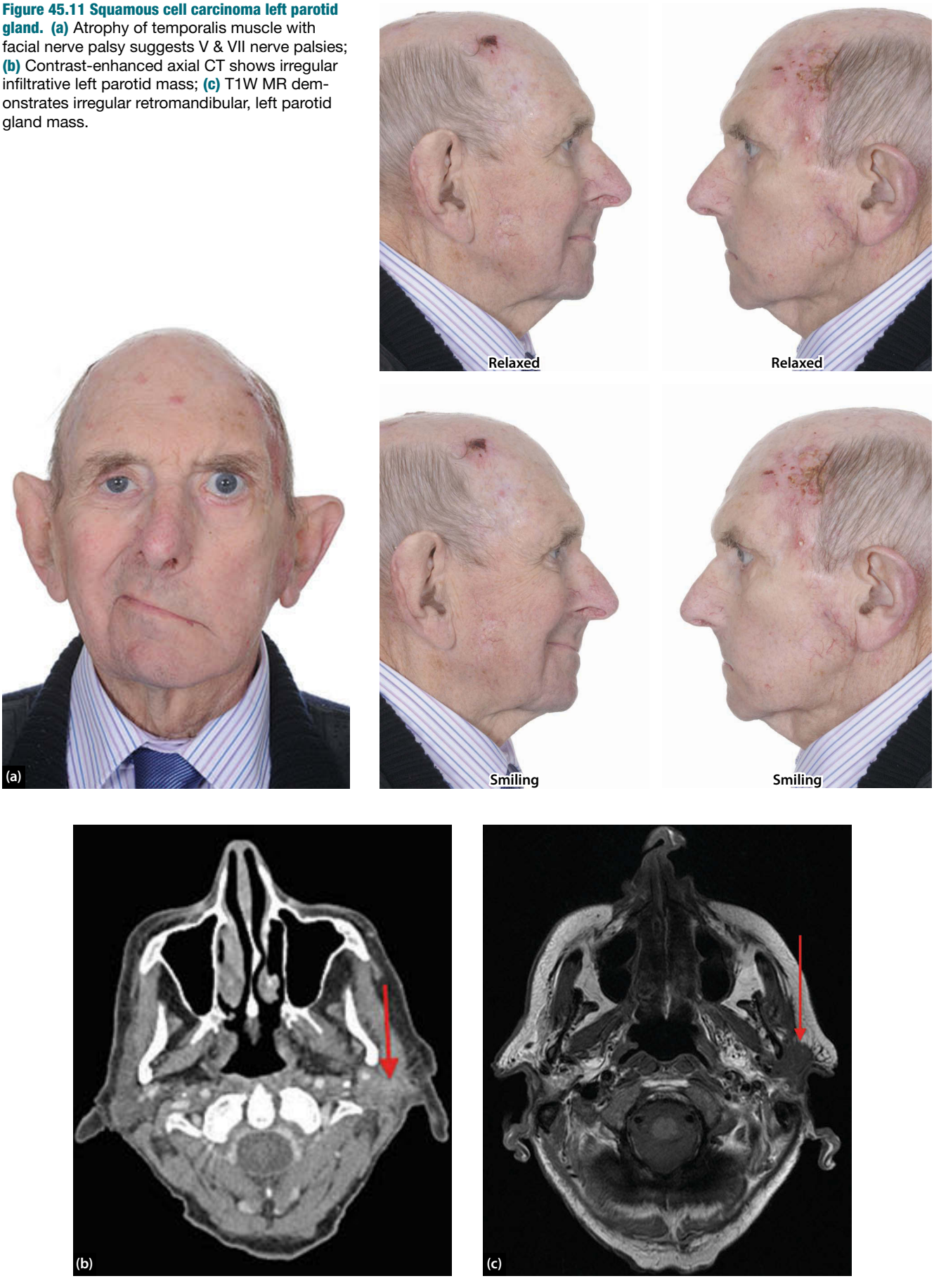
From the wider arena of oncological imaging, dynamic MRI (dMRI) continues to look at correlating enhancement patterns with angiogenesis and cellular-stromal ratios in pathological tissues. A seminal paper by Yabuuchi et al.[57] describes a promising method. Intravenous gadolinium is delivered via a power injector. Having chosen a region of interest, repeated sequential dynamic images are acquired over a period ranging from 0 to 300 seconds. Time-intensity curves (TIC) are then generated with avoidance of cystic regions and large vessel sampling. Plateau type patterns at dMRI are suggestive of malignant foci with rapid enhancement, fast peak times and delayed contrast wash-out. It is proposed that this latter finding may represent extravasation of contrast material through abnormally permeable endothelium in tumour beds.

MR proton spectroscopy can be used to characterize choline/creatinine ratios and, in 2005, King et al. showed that larger ratios imply a benign phenotype.[58]

Using combinations of these techniques, researchers are moving towards multiparametric evaluation to anticipate likely tumour behaviour, prognostics and treatment response. In 47 patients with major salivary lesions, Yabuuchi[59] retrospectively considered the added merits of combining DWI measurements with dynamic contrast-enhanced MRI. This revealed further improvements in the pre-operative separation of malignant and benign lesional characteristics with the former group illustrating rapid peak times and delayed wash-out.

At PET-CT, diffuse, supra-normal increased uptake in the salivary glands is occasionally seen incidentally in low-grade asymptomatic inflammatory disorders and connective tissue diseases. PET-CT has a well-defined role in mucosal HNSCC; however, its role in focal salivary glandular pathology is far less clear with small study sizes. The reality is that by this stage of assessment the patient would usually already have had an USgFNAC. The ability to differentiate benign from malignant disease is dependent on glycolytic activity and potential exists to misclassify hypermetabolic, benign lesions (Warthin's tumour, oncocytomas) from intermediate/low-grade malignant tumours with low metabolic activities. The real potential is for a single test to stage high-grade tumours with a propensity for occult bony metastasis.

Figure 45.11 Squamous cell carcinoma left parotid gland. **(a)** Atrophy of temporalis muscle with facial nerve palsy suggests V & VII nerve palsies; **(b)** Contrast-enhanced axial CT shows irregular infiltrative left parotid mass; **(c)** T1W MR demonstrates irregular retromandibular, left parotid gland mass.



KEY POINTS

- A specialist opinion and detailed history directs the appropriate imaging.
- US is the best initial test in most circumstances.
- Fine-needle aspiration of a mass is a robust test when good cytological support is available.
- Facial nerve symptoms or localized nodal disease is likely to signify malignant disease.

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CHAPTER 46

NON-NEOPLASTIC SALIVARY GLAND DISEASES

Stephen R. Porter, Stefano Fedele and Valeria Mercadante

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SEARCH STRATEGY

A literature search was performed using Medline and included the following keywords: non-neoplastic salivary disorders, benign salivary disorders, as well as all the main subject headings. A few earlier references are included where they are pertinent and only the relevant references have been cited.

INTRODUCTION

A wide range of non-neoplastic disorders of the salivary glands can arise, although the more common are sialolithiasis, mumps, acute suppurative sialadenitis, Sjögren's syndrome (SS) and drug-induced xerostomia. Disease of the glands typically manifests as swelling (**Table 46.1**) and/or oral dryness (**Box 46.1**). The present chapter provides an overview of non-neoplastic disorders of the salivary glands, but also focuses upon the common disorders likely to be of relevance to otorhinolaryngologists.

CONGENITAL SALIVARY GLAND DISEASE

Salivary gland agenesis

Agenesis of one or more of the major salivary glands is uncommon. There can be variation in the number of absent salivary glands and hence the degree of associated xerostomia, dysarthria and/or dysphagia varies accordingly. Lack of saliva predisposes to dental caries, gingival and periodontal inflammation, candidosis and acute suppurative sialadenitis in any existing glands, although in children severe dental caries may be the only initial sign of underlying salivary gland agenesis.[1]

The precise incidence of major salivary gland agenesis is difficult to establish due to the asymptomatic nature of many affected individuals but it may have an estimated incidence of 1 in 5000 live births,[2] with males more likely to be affected than females. Familial clustering of salivary gland agenesis has occasionally been reported but many instances are isolated, non-familial and non-syndromic.[3] Salivary gland aplasia can be associated with other ectodermal defects, in particular lacrimal apparatus abnormalities (the salivary glands and lacrimal puncta both develop at about the 4th to the 8th weeks of embryonic life as a consequence of ingrowths of ectodermal tissue into the underlying mesenchyme).[1] Autosomal dominant aplasia of the lacrimal and salivary glands is due to a defect being loss-of-function mutations in the fibroblast growth factor 10 (*FGF10*) gene at chromosome 5p13-p12125.

TABLE 46.1 Non-neoplastic causes of salivary gland swelling

Unilateral	Bilateral
• Acute suppurative sialadenitis • Recurrent parotitis of childhood • Sialolithiasis and other causes of ductal obstruction • Sjogren's syndrome (and associated non-Hodgkin lymphoma • IgG4-related disease • Sarcoidosis • Chronic non-specific sialadenitis • Xanthogranulomatous sialadenitis • Amyloidosis • Others	• Mumps • HIV salivary gland disease (and related disorders) • HCV sialadenitis • Sjogren's syndrome (and rarely bilateral non-Hodgkin lymphoma) • IgG4-related disease • Sarcoidosis • Sialosis • Pneumoparotitis • Iodine containing contrast media and radioactive iodine • Drugs (rare) • Others

BOX 46.1 Non-neoplastic causes of long-standing reduced salivary output

- Drugs (many)
- Radiotherapy of the head and neck
- Sjogren's syndrome and related disorders
- Chronic graft-versus-host disease
- IgG4-related disease
- Sarcoidosis
- Salivary gland agenesis
- HIV salivary gland disease
- HCV sialadenitis
- Others (e.g. long-standing anxiety, depression)

Associations with hypohidrotic ectodermal dysplasia (ED)[4] and lacrimal-auriculo-dentodigital (LADD; Levy-Hollister syndrome) reflecting defects of *FGF10* gene[5] and ectodactyly-ED syndromes have been reported. Bilateral parotid gland aplasia in a patient with Down syndrome has been reported[6] and agenesis of the major salivary glands in association with an absence of the lacrimal puncta of one side also observed.[7]

The management of children with absence of salivary glands follows that of long-standing oral dryness due to Sjögren's syndrome.[8]

KEY POINTS

- Lack of saliva predisposes to dental caries, gingival and periodontal inflammation, candidosis and acute infective sialadenitis, although in children rampant dental caries may be the only initial sign of underlying salivary agenesis.
- Salivary gland aplasia is rare, may occur in isolation or be associated with other ectodermal defects, in particular lacrimal apparatus abnormalities.
- The management of children with absence of salivary glands follows that of long-standing oral dryness due to Sjögren's syndrome.

INFECTIONS OF THE SALIVARY GLAND

Viral and bacterial infections are the most common infectious disorders of the salivary glands, although very rarely other infectious agents can be involved (**Table 46.2**). In addition the salivary glands may be the site of asymptomatic viral infection – particularly some of the herpes group (e.g. human herpesvirus 6 (HHV-6), cytomegalovirus and perhaps human herpesvirus 8 (HHV-8)), while saliva can contain low amounts of a wide range of infectious agents including hepatitis B virus, hepatitis C virus (HCV), HHV-8 and human immunodeficiency virus (HIV).[9, 10] There is little evidence, however, that saliva is a common fluid for the transmission of HCV or HIV.

Of note, xerostomia is more likely with viral (e.g. HCV and HIV) than bacterial infection of the salivary glands. The infections that can arise in the salivary glands are summarized in **Table 46.2**; however, as some of these are rare and/or have no specific salivary gland features, the present discussion will focus upon the more common infections of the salivary glands.

Mumps (epidemic parotitis)

Mumps is an acute generalized paramyxovirus infection of children and young adults. Mumps typically affects the major salivary glands, although involvement of other structures can occur including the pancreas, testis, ovaries, brain, breast, liver, joints and heart.[11]

Mumps is transmitted via the droplet route, and has an incubation time of approximately 14–18 days. Patients present with initial pyrexia, chills and facial pain. The parotids are typically bilaterally enlarged, although this may initially be unilateral. There is often swelling of the submandibular glands together with lymphadenopathy, giving rise to profound facial and neck swelling. Rarely sublingual swelling may be so profound as to cause elevation of the tongue and dysphagia and dysarthria. The salivary swelling tends to diminish after approximately 4–5 days and may precede more complicated aspects of the illness. There have been a small number of reports of transient facial nerve weakness in association with the parotid gland enlargement in mumps.[12]

Orchitis may develop approximately 4–5 days after the onset of parotitis. Typically only one testicle is affected, though occasionally there can be bilateral involvement. Orchitis tends to arise in post-pubertal boys, and rarely gives rise to serious long-standing disease.

Mumps can give rise to a lymphocytic or viral meningitis, which commences a few days after the development

TABLE 46.2 Infections of the salivary glands

Common	Uncommon
• Acute suppurative sialadenitis • Mumps • HIV-associated salivary gland disease • HCV-associated sialadenitis	• Human T-lymphocytic virus 1 (HTLV-1) • Epstein–Barr virus (EBV) • Cytomegalovirus (CMV) • *Mycobacterium tuberculosis* • Non-tuberculous mycobacteria • Arachna spp • *Haemophilus influenzae* • *Escherichia coli* • *Treponema pallidum* • *Eikenella corrodens* • 'Cat scratch' bacillus • Caffkiya anaerobia • *Actinomycosis israelii* • *Actinomycoses eriksonii* • *Samonella enteritidis* • *Salmonella choleraesuis* • *Histoplasma* spp • *Candida* spp • Cysticercosis

of parotitis. It should be noted that meningitis can occur in the absence of salivary gland disease. Other neurological manifestations include retrobulbar neuritis and encephalitis. Deafness is possible, but rare. Pancreatic infection may give rise to mild upper abdominal pain, but acute and long-term complications are unusual. Likewise, while cardiac, hepatic and joint infection can occur, they are rare and do not generally cause notable complications.

The diagnosis of mumps is typically based upon the clinical picture; however, it may be confirmed by detection of viral-specific immunoglobulin G (IgG) and immunoglobulin A (IgA). Viral culture is possible, but generally unnecessary as serological methods are highly sensitive.

There is no specific treatment for mumps, analgesia and appropriate fluid intake being the mainstays of therapy. It has been suggested that corticosteroids may be effective for severe parotitis, but generally these are not required unless the patients have other systemic symptoms such as orchitis.

Mumps can generally be prevented with appropriate vaccination (measles, mumps and rubella (MMR)). The effectiveness of the MMR vaccine is evidenced by outbreaks of mumps as a consequence of suboptimal uptake of vaccination.[13]

KEY POINTS

- Mumps patients present with initial pyrexia, facial pain, enlarged parotid glands usually bilateral, and swelling of the submandibular glands together with lymphadenopathy and, rarely, sublingual swelling.
- Mumps salivary swelling tends to diminish after approximately 4–5 days.
- Serious and not infrequent complications of mumps include orchitis and viral meningitis.

HIV salivary gland disease

Salivary gland manifestations can arise in up to 10% of adults and children with untreated HIV infection. Clinical syndromes of HIV infection of the salivary glands include HIV salivary gland disease per se, bacterial sialadenitis, intra-parotid lymphadenopathy, primary or metastatic non-Hodgkin lymphoma and Kaposi's sarcoma.[10] There have been rare reports of sialolithiasis possibly secondary to atazanavir (that has also been linked to renal and biliary lithiasis),[14] ranula formation of the sublingual gland[15] and submandibular gland swelling due to cytomegalovirus infection as part of immune reconstitution inflammatory syndrome (IRIS).[16]

HIV salivary gland disease is a distinct disorder characterized by recurrent and/or persistent major salivary gland enlargement and xerostomia. The parotid glands are most frequently affected, there often being profound bilateral enlargement. Submandibular gland involvement is considered to be rare.[17] Salivary gland disease tends to arise in late HIV infection, although occasionally can be the first manifestation. A higher rate of male to female ratio of involvement has been reported, but this probably reflects the epidemiology of the patients that have been previously reported. HIV salivary gland disease may be associated with HLA-DR5, and is part of a more generalized disorder termed diffuse infiltrated lymphocytosis syndrome (DILS) characterized by CD8+ T-cell infiltration of the lungs, salivary glands and lacrimal glands.[3] There is increasing evidence that salivary gland inflammation and cyst formation are driven by infection with BK polyomavirus (BKPyV) and thus, as expected, HIV salivary gland disease is a virally driven opportunistic infection in an immunodeficient host.[18, 19]

The clinical picture of HIV salivary gland mimics that of Sjögren's syndrome; however, there are distinct histopathological and serological differences between the two disorders. Patients with HIV disease generally do not have anti-Ro or anti-La antibodies – but do have hypergammaglobulinaemia. The minor salivary gland histopathology is generally similar to that of Sjögren's syndrome, being dominated by perivascular, periacinar and periductal lymphocytic infiltrates with the formation of CD20+

lymphocyte dominated lymphoepithelial islands/complex and lymphoid follicles.[20]

Multicystic lymphoepithelial lesions, sometimes termed cystic lymphoid hyperplasia (CLH) or benign lymphoepithelial lesion (BLEL) or benign lymphoepithelial cysts (BLEC), may also occur. The exact cause of the lesions is not known but it has been suggested that they are due to ductal ectasia of entrapped salivary gland inclusions arising within lymph nodes.[21, 22] Cystic change can also arise following intra-glandular ductal obstruction by hyperplastic lymphoid tissue. It is estimated that swellings associated with CLH arise in up to 6% of adults and 10% of children infected with HIV. Transformation to non-Hodgkin lymphoma is a rare complication of CLH.

The diagnostic process of HIV salivary gland disease is similar to that of Sjögren's syndrome although, unlike the latter, histopathological involvement of the minor salivary glands may not be evident in HIV salivary gland disease or CLH. Fine-needle aspiration biopsy (FNAB) is sometimes, but not always, helpful for diagnosis as it allows rapid exclusion of malignancy.[20, 23] Radiological imaging (e.g. ultrasound, computed tomography (CT) or magnetic resonance imaging (MRI) is essential to establish the cause of any swellings of salivary glands in HIV disease, and in particular to exclude the possibility of malignancy.[17]

There is little information regarding the specific management of HIV salivary gland disease and the associated cystic swellings.[17] Clinical signs are usually non-progressive, and hence therapy is only indicated if there is notable cosmetic deformity or xerostomia. While it has been suggested that anti-retroviral therapy (ART) will reduce the swelling of HIV salivary gland disease, there is more evidence that protease inhibitors of ART may increase swelling (sometimes as a consequence of far accumulation within the gland)[24] and lessen salivary secretion.[25] Other, perhaps less practical, suggested therapies are repeated aspiration, tetracycline sclerosis or surgical removal of an enlarged gland.[26] External radiation (e.g. 8–10 Gy) can cause transient improvement, although higher doses (e.g. 24 Gy) can cause resolution of disease for at least several years – without causing severe xerostomia.[27]

The salivary gland dysfunction of HIV disease increases the risk of caries and lessens quality of life, hence there is a need to lessen the symptoms of xerostomia and provide preventative oral health care.[28]

Xerostomia independent of salivary gland involvement may arise in HIV infection as a consequence of some nucleoside analogue HIV reverse transcriptase inhibitors or protease inhibitors.[25]

KEY POINTS

- HIV salivary gland disease is characterized by recurrent or persistent major salivary gland enlargement, usually of the parotid glands with or without oral dryness. It tends to arise in late untreated HIV infection and can affect both children and adults.
- Clinically it mimics Sjögren's syndrome but there is an absence of anti-Ro and anti-La antibodies in HIV salivary gland disease.

BEST CLINICAL PRACTICE

- ✓ Treatment is only indicated for notable cosmetic deformity or xerostomia.
- ✓ Anti-retroviral therapy (ART) may lessen the onset of HIV salivary gland disease and may reduce swellings.
- ✓ The swellings of HIV salivary gland disease may respond to local radiotherapy. Doses of 24 Gy may cause long-term resolution of swelling without causing severe xerostomia.
- ✓ Other suggested therapies include repeated aspiration, tetracycline sclerosis or surgical removal of an enlarged gland.

Hepatitis C virus infection

Unlike the other hepatotropic hepatitis viruses, HCV frequently gives rise to a wide spectrum of extra-hepatic manifestations that include salivary gland disease. HCV-associated salivary gland disease arises in around 80% of infected patients.[29]

Xerostomia is the predominant symptom of HCV-associated salivary gland disease[30] and objective evidence of reduced unstimulated whole sialometry has been observed in 13–33%, although some groups of patients with HCV disease seem to have normal salivary flow rates – despite the presence of HCV in saliva.[30, 31]

The histopathological features of HCV-associated sialadenitis have similarities to those of Sjögren's syndrome, there being a lymphocytic infiltrate of salivary tissue in both. Whereas the infiltrate is periductal in the latter, in HCV sialadenitis it is pericapillary. In addition there is a more dominant cytotoxic T-cell infiltrate in HCV disease than Sjögren's syndrome.[31–33]

Transgenic mice expressing HCV genes develop sialadenitis, thus confirming the notion that HCV gives rise to salivary gland disease.[34] Nevertheless, the precise pathogenesis of HCV-related salivary gland disease remains unclear, particularly as the presence of HCV RNA in saliva does not correlate with clinical or histopathological evidence of salivary gland dysfunction.[31]

HCV infection may occasionally give rise to non-Hodgkin lymphoma (usually low grade B cell tumours); indeed, the salivary glands are a common site of lymphoma in HCV-infected individuals with 'Sicca' like symptoms. There remains, however, no association between HCV infection and the pathogenesis of Sjögren's syndrome.[32]

As with other disorders that give rise to oral dryness, patients with HCV sialadenitis require treatment of the xerostomia and the associated increased risk of common oral disease such as caries and gingival inflammation.

Acute suppurative sialadenitis (suppurative parotitis; bacterial sialadenitis; bacterial parotitis)

Acute suppurative sialadenitis is an uncommon disorder characterized by painful swelling – usually of the parotid

glands (suppurative parotitis), purulent discharge from the duct of the affected gland, associated dysgeusia and cervical lymphadenopathy. When disease is severe there may be accompanying pyrexia, malaise and a risk of abscess formation.

Acute suppurative sialadenitis can affect children and adults. Prematurity may be a risk factor for disease in childhood, and sialadenitis can occur in newborns.[35–37] The highest incidence is seen in children aged 3–6 years.[38] Immunodeficiency and concurrent illness may predispose to childhood suppurative parotitis. Of interest, an aseptic sialadenitis has been observed in pre-term children receiving long-term orogastric tube feeding.

In adults, it is most commonly seen in elderly, dehydrated, patients although long-standing xerostomia (e.g. Sjögren's syndrome) and radiotherapy-induced xerostomia are additional risk factors, as well as other predisposing factors such as poor oral hygiene, diabetes mellitus, HIV disease, the placement of a Sengstaken-Blakemore tube,[39] endoscopic retrograde cholangiopancreatography (ERCP), continuous positive airway pressure therapy,[40] and the use of total parenteral nutrition. Ductal obstruction (e.g. sialolithiasis, malignancy or foreign bodies), unusual anatomy of Stenson's duct,[41] positioning of the head during long surgical procedures,[42, 43] possibly after implant placement,[44] malar augmentation with poly-L-lactic acid injections,[45] and infection as a consequence of bacteraemia may also predispose to acute suppurative sialadenitis. Coprophagia gave rise to recurrent submandibular sialadenitis in one patient. Rarely infection may be acquired nosocomially[46] and following intra-glandular injection of botulinum neurotoxin for drooling.[47]

The causative organism of acute suppurative sialadenitis is often not found; however, facultative anaerobes, particularly *Staphylococcus aureus* and *Streptococcus viridans* have frequently been reported to be of aetiological significance. In addition a wide range of other bacteria including gram negative bacilli, strict anaerobes such as *Bacteroides* spp, *Fusobacterium nucleatum* and *Peptostreptococcus anaerobius* have been identified in affected individuals.[48, 49] Rare organisms associated with acute suppurative sialadenitis include methicillin-resistant *Staphylococcus aureus*,[50] *Bartonella henselae*, *Treponema pallidum*[51] and *Eikenella corrodens*.[48] There have been rare reports of acute sialadenitis associated with primary mycobacterium tuberculosis,[52] pre-existing *Mycobacterium tuberculosis* and non-tuberculous mycobacterial infection.[53, 54] Other rare infections have included *salmonella* spp,[55] *Neisseria meningitides*, *Fusobacterium necrophorum* (Lemierre's disease)[56] and *Burkholderia pseudomallei* (Meliodosis).[57, 58] **Table 46.2** indicates other possible bacterial infections of the salivary glands.

The diagnosis of acute suppurative sialadenitis is usually straightforward – being based upon the history and clinical picture. Microbiological culture of pus, under both aerobic and anaerobic conditions, may reveal the causative agents, although specific relevant tests may be useful if a particular infection seems likely.

The benefits of sialography for the diagnosis of acute suppurative sialadenitis remain unclear. Some authorities suggest that such investigation is contraindicated (probably when there is notable disease), while others suggest that it may resolve any causative ductal stricture. Sialography may reveal areas of ductal stricture and sialectasis, the latter are most likely with recurrent disease. Scintiscanning is generally unhelpful but may sometimes reveal the underlying cause (e.g. poor salivary gland function). Ultrasound scanning is useful as it may identify sialoliths, ductal anomalies, fluid collections and parenchymal disease of probable Sjögren's syndrome or HIV disease. Additional cross-sectional imaging may be essential if abscess formation is suspected.

COMPLICATIONS

There is a risk of abscess formation as a consequence of duct ectasia, primary parenchymal involvement (most likely with submandibular gland infection) or infection of subcapsular lymph nodes.[38] Facial nerve palsy secondary to parotid abscess formation with sialadenitis is rare, but possible.[59] Extension to the neck spaces is also possible (see Chapter 40, Neck space infections).

THERAPY

Effective hydration and antibiotics are the mainstays of therapy of uncomplicated acute suppurative sialadenitis. Empirical antibiotics used are anti-staphylococcal penicillins (e.g. flucloxacillin, amoxycillin or co-amoxiclav), cephalosporins or clindamycin based on local protocols, but these may change if a causative organism is identified. Intra-ductal injection of antibiotics is unlikely to be of practical benefit. A recent literature review concluded that cephalosporins and fluoroquinolones achieve high levels of concentration in saliva and are likely to exert an effective anti-bacterial action (although, interestingly, phenoxymethylpenicillin and tertacyclines do not).[60]

Surgical drainage should be considered if there is a lack of clinical improvement after 3–5 days of antibiotic therapy, any unlikely facial nerve involvement, any involvement of deep fascial spaces, or abscess formation within the parenchyma of the gland. Superficial parotidectomy may be required if disease becomes recurrent or chronic.[61, 62]

KEY POINTS

- Acute suppurative sialadenitis presents with painful swelling – usually of the parotid glands (suppurative parotitis), purulent discharge from the duct of the affected gland, dysgeusia, cervical lymphadenopathy, pyrexia and malaise.
- Acute suppurative sialadenitis usually affects adults although children may rarely be affected. Risk factors for acute suppurative sialadenitis are centred around causes of persistent obstruction of the ductal system and/or reduced salivary production.

BEST CLINICAL PRACTICE

- ✓ The diagnosis of acute suppurative sialadenitis is primarily clinical with microbiological culture of pus, under aerobic and anaerobic conditions.
- ✓ Ultrasound imaging is probably the most useful diagnostic radiological investigation.
- ✓ Effective hydration and antibiotics are the mainstays of therapy of uncomplicated acute suppurative sialadenitis. Typical antibiotics may include anti-staphylococcal flucloxacillin, amoxycillin (or co-amoxiclav), cephalosporins or clindamycin.
- ✓ Surgical drainage should be considered if there is a lack of clinical improvement after 3–5 days of antibiotics, facial nerve, deep fascial space involvement, or abscess formation within the parenchyma of the gland.

CHRONIC NON-SPECIFIC SIALADENITIS

Chronic non-specific sialadenitis is an uncommon disorder, usually of adulthood, characterized by recurrent and/or persistent enlargement of usually one major salivary gland. The parotids are more commonly affected than the submandibular glands.[63] Patients can have episodes of disease akin to acute suppurative sialadenitis. Affected patients are generally well, have no systemic disease likely to cause sialadenitis, although many have a history of recurrent parotitis of childhood or previous sialolithiasis.

In most instances, chronic non-specific sialadenitis reflects abnormalities of the ductal system – the recurrent infection having caused or worsened any ductal strictures. Likely causes of this disorder are small sialoliths and, less commonly, external pressure and resultant ductal defects due to dentures,[64] congenital ductal defects or radiotherapy-induced salivary gland damage. The strictures have a damming action causing salivary stasis and liability to infection with resultant chronic, and possibility acute, inflammation.

The investigation of chronic non-specific sialadenitis is similar to that of acute suppurative sialadenitis, although often microbiological examination of saliva will be unhelpful clinically. Sialochemistry is not helpful. Sialography will almost always reveal strictures and/or associated distortion of the major ducts, although there can also be variable sialectasis. Imaging studies may reveal small causative sialoliths. Chronic non-specific sialadenitis has no specific histopathological features, although there may be duct dilatation (sometimes with squamous metaplasia), acinar atrophy, interstitial fibrosis and a periductal inflammatory infiltrate comprised predominantly of lymphocytes and sometimes plasma cells and eosinophils.

The clinical course of the chronic non-specific sialadenitis is highly varied; about 50% of patients have eventual spontaneous resolution of symptoms after up to 5 years, but as many as 40% will have symptoms that warrant surgical intervention.[65] Although there is a recent report of parotid duct carcinoma arising within chronic sialadenitis,[66] chronic non-specific sialadenitis does not have any notable malignant potential.

The management of any acute infection associated with chronic non-specific sialadenitis follows that of acute suppurative disease. In addition, sialagogues such as chewing gum, duct and glandular massage, improved oral hygiene and therapeutic sialography have been suggested to be useful, but there are no supporting data.[67] Unless the cause is likely to be a sialolith, subtotal or total surgical removal of the affected gland may be the only useful treatment.[62, 63, 68]

KEY POINTS

- Chronic non-specific sialadenitis is an uncommon disorder, usually of adulthood, characterized by recurrent and/or persistent enlargement of usually one major salivary gland. The parotids are more commonly affected than the submandibular glands.
- Patients can have episodes akin to acute suppurative sialadenitis but affected individuals are well and have no systemic disease likely to cause sialadenitis, although they may have a history of recurrent parotitis of childhood or previous sialolithiasis.
- Clinical course can be highly varied with up to 50% having spontaneous resolution but up to 40% may warrant eventual surgical intervention.

BEST CLINICAL PRACTICE

- ✓ Investigations might include ultrasound scanning, sialography, CT or MRI to define the ductal structure and/or identify the presence of sialoliths.
- ✓ Treat acute episodes as for acute suppurative sialadenitis with hydration and appropriate antibiotics.
- ✓ Sialagogues, glandular massage and improved oral hygiene and therapeutic sialography seem logical but there is no supporting evidence.
- ✓ Subtotal or total gland removal maybe the only useful treatment for the chronic, non-infected state unless sialoliths can be identified.

RECURRENT PAROTITIS OF CHILDHOOD (JUVENILE RECURRENT PAROTITIS)

Recurrent parotitis of childhood is characterized by recurrent parotid inflammation usually associated with non-obstructive sialectasis of the parotid gland. Recurrent parotitis can arise at any age, but the usual age of onset is 3–6 years. Childhood onset disease is usually more common in males, but interestingly, adult onset disease normally arises in females.

The disease is characterized by localized pain and swelling that may last up to 14 days. Fever and overlying erythema are common, and occasionally white mucopus can be expressed from the parotid duct. Recurrent parotitis of childhood tends to be unilateral rather than bilateral.

The number of attacks varies from 1 to 5 per year, but some patients may have up to 20 episodes of swelling per year. The frequency of recurrence tends to peak between 5 and 7 years of age, and up to 90% of patients have resolution of disease by puberty.

Sialography and ultrasonic scans reveal sialectasis, but this feature can also be observed in the non-affected glands of the opposite side. Serum amylase may be elevated.[69] The precise aetiology of recurrent parotitis remains unclear, but certainly almost all affected patients are otherwise well. There is no evidence that viral infection underlies this disorder. No gross immunological abnormalities have been described in large numbers of affected persons and there is no evidence of an associated genetic anomaly.[69]

Analgesia is the mainstay of therapy. Antibiotics do not shorten attacks. Intraductal saline with or without dilatation of Stenson's duct, intraductal antibiotics (or methyl violet to induce sclerosis) have been proposed as have included sialoendoscopy,[70, 71] ductal dilatation with a sialoballoon, but there are no reports of the outcomes of large series of treated patients. A report indicated that sialography with high concentration iodinated oil caused a 100% reduction in recurrence of juvenile recurrent parotitis of 87 patients.[72] Suggested invasive procedures include ligation of Stenson's duct, transection of chorda tympani or transection of Jacobsen nerve in the middle ear. Radical methods such as total or sub-total parotidectomy have also been proposed[72] but as the disease tends to resolve spontaneously there seem little place for such invasive measures. There is a recent report of Huangqi and bear bile capsules or granules reducing the frequency of swellings of recurrent parotitis of childhood.[73]

KEY POINTS

- Recurrent parotitis of childhood is characterized by recurrent painful unilateral parotid swelling usually associated with non-obstructive sialectasis of the parotid gland.
- The cause of recurrent parotitis of childhood is unknown although affected individuals are otherwise well.
- The usual age of onset is 3–6 years. The number of attacks varies from 1 to 5 per year, but up to 20 episodes may occur per year. The frequency of recurrence peaks between 5 and 7, and up to 90% of patients have resolution of disease by puberty.

BEST CLINICAL PRACTICE

✓ Analgesia is the mainstay of therapy. Antibiotics do not shorten attacks. A variety of other non-surgical and surgical therapies have been proposed, sialography or sialoendoscopy being the most promising of these.

IgG4-RELATED DISEASE

IgG4-related disease is a rare fibroinflammatory disorder characterized by elevated serum levels of IgG4 and multiorgan inflammation that can thus manifest with a plethora of possible manifestations. The disease has predominantly been described in Asian patients (particularly in Japan) but affected individuals have been reported in the Western World. Disease onset is usually in the 7th decade with males more likely to be affected than females (other than those with sialadenitis and dacryodenitis where there is an equal gender distribution or slight female predominance). Probable IgG4 sialadenitis has been reported in at least one child.[74]

The salivary glands are commonly affected, and in the past the features were termed 'Mikuliz disease' 'Kuttner tumour' or 'chronic sclerosing sialadenitis'. The submandibular gland is commonly affected, although the parotids, sublingual glands and minor salivary glands can occasionally be affected. The salivary gland features manifest as long-standing and generally asymptomatic swelling, sometimes, but not always, with symptoms of xerostomia.[75, 76]

The (many) other associated features of this disorder are well reviewed elsewhere[76–78] but include:

- lacrimal gland (IgG4 dacryoadenitis): swelling, keratoconjunctivitis sicca (sometimes), other features
- pituitary gland (IgG4-realted hypophysitis): headache, visual field deficits, diabetes insipidus, lactation
- thyroid (IgG4-related thyroiditis): malaise, oedema, neck swellings
- pancreas (Type 1 autoimmune pancreatitis): upper abdominal pain, obstructive jaundice, impaired glucose tolerance
- biliary tract (IgG4-related sclerosing cholangitis): obstructive jaundice
- lung (IgG4-related lung disease): cough
- prostate gland (IgG4-related prostatitis): urinary frequency
- retroperitoneal cavity (IgG4-related retroperitoneal fibrosis): fever, malaise, aortic aneurysm
- lymph nodes (IgG4 lymphadenopathy): lymph node enlargement.

Thus in specialist ENT clinics, patients may present with symmetrically swollen upper eyelids, salivary glands, cervical lymphadenopathy[79] and sometimes symptoms of ocular and/or oral dryness.

Histopathological examination of IgG4-related sialadenitis salivary gland lesions reveals a dense lymphoplasmacytic infiltrate, large irregular follicles with expanded germinal centres and acinar atrophy. Obliterative phlebitis, in which there is obliteration of venous channels by the lymphoplasmacytic infiltrate, is said to be a characteristic feature as is storiform fibrosis,[80] although this last feature may not always be evident in affected salivary glands.[81] Unlike Sjögren's syndrome there is an absence of lymphoepithelial lesions in IgG4-related sialadenitis. Immunohistochemistry of affected salivary gland tissue of IgG4-related disease reveals an abundance of IgG4+ plasma cells that may constitute up to 50% of the plasma cell infiltrate (although this may be absent if there is extensive fibrosis). The normal lobular architecture of the glands are usually preserved and the inflammation may be localized to one site or throughout a gland.[75]

There may be a hypergammaglobulinaemia and serum levels of IgG4 are always elevated and there is an absence

of circulating anti-Ro and anti-La antibodies.[76] In view perhaps of the sometimes non-diffuse nature of the disease within salivary glands, sialography may not always demonstrate any notable ductal abnormalities, although punctate of globular sialectasis may sometimes be observed.[82] Ultrasound scanning may reveal salivary gland enlargement and hypoechoic areas[82] while MRI may similarly demonstrate salivary gland swelling, but may not delineate the nodal (i.e. hypoechoic) areas.

The aetiopathogenesis of IgG4-related disease is reviewed well elsewhere.[76, 78, 80] The precise cause or trigger of this fibrotic disorder is not known although disease is driven by an excess production of type 2 T-helper cells and regulatory T-cell cytokines (e.g. IL-10) and transforming growth factor (TGF) -β, the latter then driving fibrosis.

There are no randomized controlled trials (RCTs) of the management of the oral aspects of IgG4-related sialadenitis and where disease is asymptomatic no therapy may be warranted. Short-term glucocorticoids may cause an increase in saliva production in affected patients.[83] This response contrasts with that of Sjögren's syndrome and may reflect the possibly localized involvement of the salivary glands in IgG4-related disease. Azathioprine or calcineurin inhibitors have been employed for some of the non-salivary elements of IgG4-related disease and, perhaps as expected, rituximab has been reported to reduce the salivary gland swelling of a small number of patients.[84, 85] Surgical excision of an affected gland is often advocated.[86]

Malignancy can arise in patients with IgG4-related disease (including one report of an unspecified cancer of the tongue) but there is no evidence that the risk of malignancy at any likely site of IgG4 related disease is increased in comparison to that of appropriate control populations.[87]

KEY POINTS

- IgG4-related disease is a multiorgan fibroinflammatory disorder that can give rise to painless enlargement, sometimes with dysfunction of the submandibular and other major salivary glands.
- Disease usually arises in middle to late life. The diagnosis typically rests upon the presence of elevated serum levels of IgG4 and histopathological evidence of a lymphoplasmacytic infiltrate with a high percentage of IgG4+ cells and the presence of fibrosis. Ultrasound scanning may demonstrate multiple hypoechoic areas.
- There is no evidence that IgG4 disease increases the risk of malignancy of the salivary or lacrimal glands.

BEST CLINICAL PRACTICE

- ✓ While IgG4-related sialadenitis has some of the clinical features of Sjögren's syndrome, the serological, histopathological and radiological features of the two disorders are distinctly different.
- ✓ Surgical excision of affected salivary glands may be helpful, as may high dose systemic corticosteroids. Patients with multiorgan disease may benefit from systemic immunosuppression. The long-term outcomes of IgG4-related disease are presently not known.

Xanthogranulomatous sialadenitis

Xanthogranulomatous sialadenitis is a very rare disorder manifesting itself as a solitary painless swelling within a major salivary gland.[88] It is histopathologically characterized by the presence of lipid-laden macrophages (xanthoma cells or foamy macrophages) with chronic and acute inflammation as well as non-caseating granulomas. The investigation of this disorder is similar to that of a salivary gland malignancy. It has been suggested that xanthogranulomatous sialadenitis may arise as a consequence of FNAB, but there are few supporting data. Excision would seem to be the logical treatment, particularly in view of the presence of Warthin's tumour in association xanthogranulomatous sialadenitis of one patient.[89, 90]

Sialolithiasis

Sialolithiasis is a common disorder characterized by the formation of a calculus (sialolith) usually within the ductal system of a gland. Sialoliths can arise in both the major and minor salivary glands – indeed, necropsy studies revealed that 1% of submandibular glands can have sialoliths while sialomicroliths (microscopic stones/concretions) are present in almost all submandibular, and some parotid glands. Sialoliths are more common in the submandibular glands (e.g. 83% of one sample) than the parotid (10%) or sublingual (7%) glands,[36] and are more common in females than males, and are much more likely in adults than in children. The minor salivary glands, particularly of the upper lip, can be affected.[91]

Sialolithiasis does not always give rise to clinical signs or symptoms, indeed the presence of sialoliths on ultrasound scans of salivary glands of patients without clinical problems is not uncommon.[72] Obstruction of a major duct will give rise to pain and swelling, typically in the submandibular gland, with gustation or eating. The swelling is diffuse, develops rapidly and is often associated with a burning-like local pain. The swelling is generally non-tender and gradually resolves over a few hours. Longstanding sialolithiasis may give rise to acute suppurative sialadenitis or chronic non-specific sialadenitis. Sialoliths of minor salivary glands give rise to painless hard swellings that rarely form mucoceles.

The likely cause of sialolith formation remains unknown,[92] although stasis caused by sialomicroliths, with resultant inflammation and fibrosis and further stagnation of calcium-rich fluid can be a driver for sialolith formation. However, sialomicroliths need not be the origin of all sialoliths. The sialoliths are composed of both organic and non-organic material, the central medulla being the more organic. The high proportion of sialoliths in the submandibular gland possibly reflects the high alkalinity and calcium content of submandular saliva together with its strong parasympathetic secretory drive. Calcium phosphate is the predominant salt of the calculi, laid down as concentric shells of about 10 micrometres thickness.

It is suggested that sialoliths may be associated with diabetes mellitus, hypertension and/or chronic liver

disease, and possibly nephrolithiasis,[93] but not to water hardness.[94] Patients with hyperparathyroidism may have an increased incidence of sialolithiasis, and individuals with both hyperparathyroid disease and sialolithiasis have a greater risk of nephrocalcinosis than those without sialolithiasis.[93] An association between the anti-HIV agent atazanavir and sialolithiasis has been reported.

INVESTIGATIONS

Plain radiographs (e.g. lateral skull and occlusal views for suspected submandibular stones) may reveal a sialolith – provided it is large and radiopaque. However, as many as 30% of sialoliths, particularly of the parotid glands, are radiolucent. Ultrasound scanning can detect both radiopaque and radiolucent sialoliths (see Katz et al.[72] for useful review). Sialography may also be helpful but can be technically difficult when investigating the submandibular gland. Pan-oral tomograms are not helpful in view of their tomographic nature, although CT and possibly MRI may be of some benefit. Where available, sialoendoscopy (SE) may be a first-line investigative tool.

TREATMENT

When small and accessible, it may be possible to express a sialolith from the submandibular duct by manual palpation, and many sialoliths can also be simply removed via a transoral approach – if within the anterior segment of the submandibular duct.[95, 96] This does, however, carry a risk of stricture formation.[97] Transcervical surgical removal of an affected gland can often be the only effective treatment for calculi in the posterior aspect of the duct or within the gland, particularly when there is lithotripsy and/or sialoendoscopic methods are not available (see below). A submental approach that lessens postoperative scarring, provides good cosmetic outcomes and is no more time consuming than other approaches has also been suggested.[98]

The management of sialolithiasis has been significantly advanced by the introduction of minimally invasive, gland-sparing, therapies, which can often be undertaken under local anaesthesia in children and adults.[99, 100] These methods include interventional SE (that includes endoscopy plus possible laser cutting of intraductal fibrosis), with or without extracorporeal shock wave lithotripsy (ESWL) – although ESWL is not available in the US. Interventional SE may be used for both diagnosis and treatment, and the latter is particularly useful for small distal sialoliths, particularly when there are multiple stones. When SE is unsuccessful for small distal sialoliths, or the sialolith is proximal, mobile or intraparenchymal there may be a need for ESWL followed by SE (with basket retrieval of the fragments). Sialoliths of up to 10 mm will require ESWL and SE and there may be a need for an open surgical approach.[101] Intracorporeal lithotripsy (i.e. sialolith fragmentation with XeClexcimer, flash-lamp pulsed dye, Ho:YAG or erbium:YAG) is now possible as the fibres of the lasers are of small diameter,[102] but the lasers are expensive, the procedure is time-consuming and there is a risk of perforation of the duct and possible abscess formation that will necessitate surgical removal of the gland.[100]

The majority of studies of minimally invasive therapy of sialolithiasis have been of submandibular disease. However, these techniques seem to be equally applicable to parotid sialoliths.[103] The outcomes of interventional sialoendoscopic methods are highly favourable. Surgeon-based results report sialolith removal being achieved in up to 93% of patients and relief of symptoms being reported by up to 95%.[102, 104] Patient-orientated outcomes of minimally invasive procedures report resolution in 86% of patients with sialolithiasis and a significant improvement of quality of life and in the Glasgow Benefit Inventory (GBI).[105] Significant adverse side effects such as upper airway obstruction are rare.[106] Minimally invasive procedures are also applicable to the management of ductal obstruction due to stenosis and mucous plugging.[107–109] Minimally invasive methods are increasingly available across the globe, although the equipment is costly and, as with all new surgical procedures, there is a need for clinicians to be appropriately trained to lessen operating times, minimize morbidity and ensure that surgeon- and patient-reported outcomes are high.

Preliminary data suggest that systemic therapy with the alpha-1-blocker alfuzosin may reduce symptoms associated with ductal stenosis of the parotid gland or post-lithotripsy therapy of parotid sialoliths[110] but there is a need for prospective studies to confirm the exact benefits of this treatment.

KEY POINTS

- Sialolithiasis is a common disorder due to formation of calculi (sialoliths) usually within the ductal system of a gland.
- Sialoliths are more common in the submandibular glands (e.g. 83% of one sample) than the parotid (10%) or sublingual (7%) glands, are more common in females than males, and are much more likely in adults than in children.
- Sialolithiasis presents as pain and swelling, typically in the submandibular gland with gustation or eating. The non-tender swelling is diffuse, develops rapidly, is often associated with a burning-like local pain and resolves over a few hours.
- Long-standing sialolithiasis may give rise to acute suppurative sialadenitis or chronic non-specific sialadenitis.

BEST CLINICAL PRACTICE

- ✓ Investigations include plain radiographs and ultrasound scanning. Sialoendoscopy, where available may also be useful.
- ✓ When small and accessible, manual expression of a stone from the submandibular duct is often feasible, and many can also be removed surgically if within the anterior segment of the submandibular duct, but this carries a risk of stricture formation.
- ✓ Minimally invasive procedures such as sialoendoscopy with or without extracorporeal lithotripsy would seem the highly effective for the removal of many sialoliths.
- ✓ Surgical removal of an affected gland may, however, be the only effective treatment for some cases of sialolithiasis.

OTHER INFLAMMATORY DISORDERS

Chronic sarcoidosis can give rise to xerostomia and salivary gland enlargement in up to 9% of affected patients, which often occurs as part of Heertfordt's syndrome.[111] Parotid gland swelling can also arise (sometimes in association with facial nerve palsy)[112] and while the swelling is usually unilateral, there have been reports of bilateral parotid gland enlargement in sarcoidosis.[113] Reports of Crohn's disease affecting the minor salivary glands[48] are probably unexpected, in view of the widespread nature of oral lesions of the disorder; however, involvement of the major glands is rare. Major salivary gland enlargement due to Wegener's granulomatosis[114] has been reported but again is rare.

DRUG-ASSOCIATED SALIVARY GLAND DISEASE

A wide range of drug-related salivary disorders can arise. These predominantly comprise swelling and/or xerostomia (**Table 46.3**).[115]

Salivary gland swelling due to iodine-based agents

Mild acute sialadenitis (sometimes termed 'iodide mumps') can arise in response to iodine-based contrast media (e.g. for percutaneous coronary interventions).[116–118] This disorder tends to be transient.

Radioactive iodine, used for the treatment of thyroid cancer, can cause transient sialadenitis; indeed, sialadenitis is the most frequent non-thyroid complication of radioactive iodine therapy. This sialadenitis manifests itself as transient xerostomia, and unilateral or bilateral salivary gland enlargement, the parotid being particularly affected.[119] The clinical features develop within 24 hours of iodine therapy and are suggested to resolve within a week. However, inflammation may persist, particularly when doses of radiation have been high, and cause permanent loss of function of one or more glands and give rise to pain and reduced swallowing.[120, 121] One study found that 20% of 852 major salivary glands of 213 patients who had received high dose radioiodine therapy had scintigraphic evidence of reduced function, with good correlation between symptoms of xerostomia and degree of salivary gland dysfunction (particularly when the submandibular glands were affected).[122] The risk of long-term symptomatic sialadenitis secondary to iodine 131 (I-131) may possibly be predicted from sustained high salivary gland-to-background uptake ratio (SUR) of I-131 as demonstrated with scintigraphy of post-therapy glands.[123]

The risk of radioactive iodine-induced sialadenitis can be reduced by use of lemon confectionary – these increase salivary flow, increasing the speed of carriage of radioactive iodine through the glands and hence reducing the time of glandular radiation exposure. There are recent reports of sialoendoscopy being an effective procedure for patients with long-standing sialadenitis of the parotid or submandibular glands secondary to radioiodine therapy, the sialadenitis being due to mucous plugs, ductal debris and/or stenosis.[124] It has been suggested that thymus honey may be a means of lessening sialadenitis of radioiodine, but there is no supportive evidence.[125]

TABLE 46.3 Salivary gland manifestations of drug therapy

Xerostomia	Salivary gland swelling	Sjogren's syndrome	Salivary gland pain	Saliva coloured red
• Atropine and analogues (antimuscarinics) • Tricyclic antidepressants • Serotonin re-uptake inhibitors (SRIs) • Antihistamines • Antiemetics • Tranquillizers (antipsychotics) • Decongestants • Bronchodilators • Appetite suppressants • Amphetamines • Lithium • Omeprazole • HIV protease inhibitors • Disopyramide • Dideoxyinosine • Didanosine • Diuretics • Interleukin-2 • Retinoids • Others	• Anti-thyroid agents • Chlorhexidine • Cimetidine • Clonidine • Ganglion-blocking agents • Insulin • Interferon • Iodides • Isoprenaline • Methyldopa • Nicardipine • Nifedipine • Nitrofurantoin • Oxyphenbutazone • Phenothiazines • Phenylbutazone • Ritodrine • Sulphonamides	• Hydralazine • Levamisole • Practolol • Procainamide • Sucralfate	• Bethanidine • Bretylium • Clonidine • Cytotoxics • Guanethidine • Methyldopa	• Rifabutin • Rifampicin

Salivary gland swelling due to other agents

A wide range of non-iodine-based drugs has been suggested to give rise to transient painful swelling of the salivary glands, and in particular the parotid glands. A recent systematic review of 84 case reports of drug-induced parotitis (i.e. swelling and pain) concluded that l-asparaginase, clozapine and phenylbutazone would seem to be the most likely agents to cause medication-associated swelling of the parotid (and presumably other major) salivary glands.[115] However, many other drugs have probably also given rise to parotitis and include: methyldopa, IFN-α, oxyphenbutazone, ramipril, trimethoprim/sulfamethoxazole, nicardipine, nifedipine, chlormethiazole, methimazole, naproxen, nitrofurantoin, sulfadiazine, captopril, cytarabine, cimetidine, ranitidine and thioridazine.[115, 126] Protease inhibitors of HIV may cause bilateral salivary gland enlargement. Bilateral sialadenitis observed in one adult following naproxen therapy was thought to be allergic in origin as the affected patient also had a cutaneous rash. Salivary gland swelling has been reported in one patient with organophosphorus poisoning.[127]

KEY POINTS

- Mild transient, bilateral, painless sialadenitis may arise with a number of drugs, particularly l-asparaginase, clozapine and phenylbutazone.
- Transient sialadenitis secondary to radioiodine is not uncommon and 20% of patients can develop long-standing symptoms that may warrant sialoendoscopic intervention.
- A wide spectrum of other drugs can cause salivary gland enlargement.

XEROSTOMIA

Dry mouth is a common complaint in many elderly persons.[128–130] This is a probably a consequence of a large number of drugs (more than 500) that can cause xerostomia and the high frequency of polypharmacy in the elderly. The principal mechanism of drug-induced xerostomia reflects anticholinergic or sympathomimetic actions, hence the drugs most commonly implicated in xerostomia are tricyclic antidepressants, benzodiazepines, atropinics, beta-blockers and anti-histamines, and thus it is common in patients treated for hypertensive or mental illness (**Table 46.3**). While often promoted as having less anticholinergic actions than the tricyclics, the serotonin reuptake inhibitors (SRIs) still cause some dry mouth. Some other newer drug therapies, including omeprazole, anti-HIV protease inhibitors, the nucleoside analogue HIV reverse transcriptase inhibitor didanosine, trospium chloride, elliptinium, tramadol and new generation antihistamines, may all cause drug-induced xerostomia.

Some drugs can give rise to primary Sjögren's syndrome-like disease. These include hydralazine, Busulfan, quinidine sulphate and thiobendazole; however, this clinical disease can be transient. In addition, affected patients may not have high levels of immunological markers of Sjögren's syndrome, hence it seems unlikely that this is true Sjögren's syndrome.[131]

KEY POINTS

- There are more than 500 drugs that can cause dry mouth but the principal mechanism of action of xerostomia is anticholinergic and sympathomimetic; therefore, tricyclics, benzodiazepines, atropinics, beta-blockers and anti-histamines are the commonest culprits.
- Drugs may also give rise to salivary gland swellings.

SOME DISORDERS ASSOCIATED WITH ORAL DRYNESS

Radiotherapy-associated salivary gland dysfunction

Xerostomia is the most common complaint of head and neck cancer survivors that have received radiation therapy, with a prevalence of 93% during radiotherapy (RT) and 74–85% following RT.[132] The prevalence of RT-induced xerostomia varies with respect to RT field, dose, regimen and technique. The introduction of intensity-modulated radiation therapy (IMRT) has led to a significant reduction in the prevalence of xerostomia after RT. A recent systematic review comparing the effect of different techniques of RT on xerostomia scores confirmed a significant overall benefit in favour of IMRT with a hazard ratio of 0.76 (95% CI: 0.66, 0.87; $p < 0.05$).[133]

Radiation-induced xerostomia and hyposalivation typically commence early during treatment: during the first week after exposure to 10 Gy, a 30–50% decrease in salivary flow can be observed;[134] after 7 weeks of conventional RT (70 Gy), salivary flow can diminish to approximately 20% of the baseline flow rate.[135] Radiation-induced salivary gland dysfunction is considered irreversible,[136] although a slight recovery of salivary function 12–18 months after treatment completion has been reported.[137]

Two separate mechanisms seem to cause radiation damage to salivary glands. The first mechanism involves selective cell membrane damage resulting in altered intracellular signal transduction and defects in cellular functioning.[138, 139] The second mechanism includes the loss of secretory cells as a result of progenitor cell death.[140]

Whatever the mechanism, the impact of RT-associated hyposalivation upon the mouth and patient well-being can be significant. The rapid reduction in saliva gives rise to dysarthria, dysgeusia, difficult mastication and dysphagia. The inhibition of taste sensation and the impairment of chewing and swallowing can adversely impact upon a patient's nutritional status. Patients may experience intraoral burning sensation and an increased sensitivity to salty and spicy foods. Wearing dentures may be extremely

uncomfortable due to the reduced surface tension between the dry mucosa and the prosthesis.[141] Clinically the lips can become dry, desquamated and fissured, and the oral mucosa atrophic, pale and hyperemic. Patients with long-standing RT-induced xerostomia have an increased risk of caries, oral candidal infections (e.g. acute pseudomembranous candidiasis, angular cheilitis and median rhomboid glossitis) and acute suppurative sialadenitis of the parotid glands.[132, 142, 143]

PREVENTION OF RT-INDUCED HYPOSALIVATION

There remains no means of reversing any RT-induced damage of the salivary glands, although IMRT has reduced the frequency and severity of this complication. Several additional strategies have been proposed to prevent RT-induced salivary damage, particularly the use of the radioprotectant amifostine. A meta-analysis in 2006 of four investigations concluded that amifostine is effective in reducing the chances of developing Grade 2–3 acute xerostomia and late xerostomia by 76% and 67% respectively ($p < 0.05$) compared to placebo.[144] Two later randomized trials confirmed these findings,[145, 146] but two other studies failed to demonstrate a reduction in the incidence of acute and late xerostomia in participants receiving concomitant chemoradiotherapy and amifostine.[147, 148]

Intravenous amifostine can cause adverse side effects such as hypotension (62% of patients) and nausea, which seem to occur less frequently when amifostine is administered subcutaneously.[149] There is no evidence to suggest that amifostine may have a tumour-protective activity and reduce efficacy of anti-cancer therapy.[150] As all of the randomized studies of amifostine involved patients who were receiving conventional RT, is not clear if the addition of amifostine to IMRT is beneficial in reducing xerostomia.

There have been seven randomized double-blind placebo controlled trials investigating the effect of pilocarpine in preventing the incidence of xerostomia when administered during the course of RT and up to 3 months after. Four RCTs showed no significant difference between treatment and placebo groups with respect to xerostomia,[151–154] although a significant improvement in both subjective and objective outcome in treatment versus placebo was observed in others.[155, 156] Scarantino reported a moderate improvement in the average unstimulated salivary flow in the pilocarpine group (P value < 0.05), whereas no difference was noted following parotid stimulation or with regard to subjective outcome.[157] However, detailed information on dose distribution – the most important prognostic factor for developing salivary dysfunction – was generally lacking in the reports of the RCTs. As a consequence, there remains little robust evidence to suggest efficacy of pilocarpine in preventing xerostomia and hyposalivation associated with RT.

A phase II study suggested that following submandibular gland transfer out of the main RT field (to the submental space) 81% of patients had no or minimal xerostomia at the end of RT. Similar results were reported by Zhang et al.[158] A multicentre phase III comparative randomized trial reported better outcomes of submandibular salivary glands transfer with respect to prophylactic pilocarpine[159] in terms of xerostomia reduction. Surgical complication associated with this technique include facial oedema (13.6%), submental swelling (19%), shoulder weakness (4.5%) and neck numbness (6.8%).[160] The long-term efficacy of this approach has been demonstrated in a non-randomized study by Liu et al.[161] However, this invasive procedure is only applicable to patients with cancers requiring surgical resection as part of their treatment and it remains invasive, expensive and time-consuming.[162]

A recent randomized feasibility trial of the potential benefit of acupuncture showed that the individuals receiving acupuncture concurrently to RT had significantly lower xerostomia scores and greater salivary flow rate than the group randomly assigned to receive standard care.[163] The results were in agreement of another small study.[164] At present there remains no good evidence that acupuncture is an effective means of reducing the risk of RT-associated xerostomia.

MANAGEMENT OF RT-INDUCED HYPOSALIVATION

The management of RT-induced salivary gland hypofunction remains challenging, as there is no means of reversing the salivary gland damage. There are a number of promising modalities, but their long-term efficacy requires to be appropriately determined.

Sialagogues

Patients often suck confectionary or chew gum to lessen any oral dryness, but these have only short-term, if any, benefit and can increase the risk of caries if they contain sucrose.

The parasympathomimetic muscarinic secretagogues pilocarpine and cevimeline have been used to treat the xerostomia. Pilocarpine is a relatively non-selective muscarinic receptor agonist whereas cevimeline is an acetylcholine analogue that selectively stimulates the M3 muscarinic receptors in salivary glands.[165]

Cevimeline is not commercially available in Europe but has been shown to increase salivation after head-and-neck irradiation in animal studies and in two RCTs involving human patients. In dosages of 30 mg three times daily, cevimeline-treated subjects had significantly greater increase in the unstimulated salivary flow rate, but not stimulated, than patients receiving placebo. The subjective sensation of xerostomia, assessed via visual analogue scale (VAS) and questionnaire, improved in the cevimeline group but only in one study.[166] In a recent double-blind multicentre, randomized, placebo-controlled study, using the same dosage of cevimeline daily, the investigators observed that the grade of xerostomia decreased for both cevimeline-treated and placebo-treated patients over the course of the treatment.[167]

Six randomized double-blind trials have investigated the efficacy of pilocarpine in the treatment of radiation-induced dry mouth. The majority of these studies reported that pilocarpine (15 mg to 30 mg per day) is effective in lessening the sensation of oral dryness (measured by a VAS) and increasing salivary flow rate in post-RT setting, although adverse side effects are frequent, dose-dependent and can be problematic.[168–173] Topical pilocarpine (spray or lozenge) has been introduced in the attempt to minimize adverse side effects; results of clinical trials were, however, disappointing and did not encourage further investigations.[174, 175]

Oral mucosal lubricant/salivary substitutes

A wide variety of salivary substitutes are commercially available across the globe for the management of xerostomia of any cause. Available salivary substitutes are characterized by different composition and viscosity; they contain mucin, carboxymethylcellulose, hydroxyethylcellulose, xanthan gum, linseed or polyethylene oxide. While these agents may lessen symptoms transiently they have no lasting beneficial effects. The majority of studies of the efficacy of these agents have included a small numbers of patients, have rarely been well-designed RCTs and have had a variety of different end points. As a consequence a recent Cochrane review concluded that no salivary substitute could be recommended for the treatment of long-standing oral dryness of any cause.[176] The major disadvantages of salivary substitutes consist of their transient temporary activity, taste, excessive viscosity and cost. About 40% of patients discontinue the use of saliva substitutes and prefer to sip water as required.[177]

Other strategies

Although some available studies suggested acupuncture could provide symptomatic relief, three independent systematic reviews concluded that there remains insufficient evidence to support acupuncture as a standard treatment for RT-induced dry mouth.[178–180] More recently a multicentre randomized crossover study found that acupuncture, compared with oral care, produced significant reductions in patient reports of severe dry mouth, but no significant changes in either stimulated or unstimulated saliva measurements over the treatment.

A Phase I study of transfer of the *Aquaporin 1* (*Aqp1*) gene via retroductal cannulation of the parotid glands demonstrated an early positive response to adenoviral-mediated *Aqp1* cDNA transfer to a single previously irradiated parotid gland. Six of 11 patients had enhanced parotid flow rates and reduction in dry mouth symptoms.[181]

Electrostimulation of salivary glands via the lingual nerve has been demonstrated to reduce the symptoms of dry mouth and increase salivary flow.[182, 183] The effect of an intra-oral electrostimulating device is presently being assessed in a large RCT of patients with RT-induced salivary dysfunction.

KEY POINTS

- Radiotherapy of head and neck malignancies can cause profound oral dryness and salivary gland acinar destruction when the radiotherapy is directed through the major salivary glands.
- The degree of xerostomia reflects the duration and dose of radiotherapy.
- The xerostomia is irreversible and patients have oral symptoms akin to those of Sjögren's syndrome.

BEST CLINICAL PRACTICE

- ✓ Double blind, randomized controlled trials have conclusively established that oral and perhaps high dose topical pilocarpine may reduce the frequency and severity of radiotherapy-induced xerostomia and associated symptoms.
- ✓ IMRT reduces the frequency and severity of long-term salivary gland hypofunction.
- ✓ Radioprotectants such as amifostine may be of advantage in preventing radiotherapy-induced xerostomia.
- ✓ There remains no effective means of reversing or reducing the effects of established RT-associated xerostomia although a number of potentially promising therapies are presently in trial.

Sjögren's syndrome

Sjögren's syndrome is the second most common autoimmune connective tissue disorder, characterized by xerostomia and xerophthalmia due to profound lymphocytic infiltration into the salivary and lacrimal glands.[184]

Sjogren's syndrome can be broadly classified as primary disease of which there are only symptoms and signs affecting the eye and mouth, and secondary Sjögren's syndrome in which there is xerostomia, xerophthalmia and associated connective tissue disorder – most frequently rheumatoid arthritis or systemic lupus erythematosus. This classification is possibly more simplistic, as many patients with primary Sjögren's have a spectrum of other systemic, and often autoimmune phenomena.

Sjogren's syndrome occurs in 0.2%–3% of populations, seems to have no geographic or ethnic associations but is possibly nine times more common in women than men. Disease is usually detected in the 4th–6th decade of the patient's life, although Sjögren's syndrome can arise in younger adults and occasionally in children under 10 years of age. Sjögren's syndrome probably remains underdiagnosed, possibly reflecting the generally mild nature of the clinical signs in some patients. In addition, there is an increasingly wide range of other disorders that may give rise to clinical features similar to those of Sjögren's syndrome – notably infection with HIV, HCV and chronic graft-versus-host disease. Many asymptomatic people have circulating ANAs relevant to Sjögren's syndrome, but these are generally present in low titre and are not indicative of a future risk of Sjögren's syndrome.

The clinical manifestations of Sjögren's syndrome are well detailed elsewhere[185] and for the purposes of this text, only the oral and salivary features of Sjögren's syndrome

will be discussed. Nevertheless it is important to appreciate that primary disease can give rise to arthralgia (in 75% of patients) and myalgia (45%); that each may arise before the onset of lacrimal or salivary gland symptoms, xerosis (30%), vasculitic and other cutaneous rashes; and that up to 15% of patients may have Raynaud's phenomenon.[185] Thus, like secondary Sjögren's, the primary disease can significantly impact upon the function, well-being and quality of life of affected individuals.

The oral dryness of Sjögren's syndrome (both primary and secondary) can be profound, giving rise to dysarthria and dysphagia. The oral dryness leads to retention of food on the teeth, mucosa and gingiva and thus increases the frequency of caries (particularly cervical disease) and acute gingivitis. Patients with Sjögren's syndrome do not appear to have an increased predisposition to periodontitis per se.

There is an increased liability to candidal infection, notably acute pseudomembranous candidiasis, and median rhomboid glossitis, chronic atrophic candidiasis (denture-associated stomatitis) and angular cheilitis. The long-standing oral dryness of Sjögren's syndrome increases the liability to acute suppurative parotitis.

The poor salivary output can lead to dysgeusia and loss of taste – many affected persons report most foodstuffs taste 'cardboard-like'.

Affected patients may have intermittent swelling of the major salivary glands – notably the parotid glands, this often reflects non-specific inflammatory change within the glands. Solitary enlargement of a salivary gland may reflect chronic sialadenitis, acute suppurative parotitis and, importantly, non-Hodgkin lymphoma.

Sjogren's syndrome is a potentially malignant disorder having a 4.3% risk of malignancy with a standardized incident rate of 18.9. Low-grade marginal-zone lymphoma related to mucosa-associated lymphoid tissue (MALT) is the common lymphoma but others can also be follicle-centre, diffuse B cell lymphoma (DBCL) or lymphoplasmacytoid lymphoma.[186, 187] Risk factors for malignancy in Sjögren's syndrome include splenomegaly, lymphadenopathy, salivary gland enlargement(s), low C4, high β-2 microglobulin, low CD4 T-cells, low IgM and mixed cryoglobulinaemia. Therapy is usually cyclophosphamide, doxorubicin, vincristine, prednisolone (CHOP) and the outcomes are extremely good, with the 5-year survival rates being 85–100%.

The aetiopathogenesis of Sjögren's syndrome is complex and the precise cause, like many other autoimmune connective tissue disorders, remains unknown. There may be some genetically determined risk factors for its development, but while HIV and HCV infection may give rise to some of the histopathological and clinical features of Sjögren's syndrome, there is no evidence that this autoimmune disorder has an infectious aetiology. Similarly, the malignancies of Sjögren's syndrome are also not thought to be driven by viral or other infections.

DIAGNOSIS

The diagnostic criteria (and hence the relevant investigations) have been subject to considerable debate over the last 10 years. Until recently, there were the American European Consensus Group (AECG) criteria and the American College of Rheumatology (ACR) criteria. A detailed critique of these is available elsewhere[188] but essentially the two systems comprised generally similar diagnostic steps of detection of clinical symptoms and signs of lacrimal and salivary gland dysfunction, specialized investigation of lacrimal and salivary gland structure and function (e.g. radiological and histopathological investigations), the presence of circulating antibodies (anti-Ro and anti-La) and the exclusion of other disorders likely to give rise to a similar clinical picture (e.g. HIV or HCV disease, sarcoidosis, chronic graft-versus-host disease, IgG4 disease and perhaps, although very rarely, amyloidosis).

The AECG classification was the most widely accepted system and formed the basis of the diagnosis of Sjögren's syndrome in possibly the majority of major units across the globe. It was based on the presence of two subjective and two objective criteria of dryness, a salivary gland biopsy grade 3 or 5, and the presence of relevant circulating autoantibodies.[188] Although the AECG classification took into consideration only anti-SSA/-SSB antibodies (Anti-Ro/La), perhaps as expected a number of other autoantibodies are frequently detected in patients with Sjögren's syndrome. The most frequent autoantibodies are antinuclear antibodies (ANA), in up to 80% of the patients, and rheumatoid factors (RF).[189] According to the AECG criteria, salivary gland function could be assessed by unstimulated whole salivary flow, parotid sialography or salivary gland scintigraphy. However, it was shown that the addition of salivary gland ultrasonography can significantly improve the diagnostic performance of the AECG criteria. However in 2016 a unified system was agreed – the American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) criteria – that is based upon a scoring system, based upon objective features of LGB histopathology, presence of anti-Ro/La, ocular staining score, Schirmer test and whole saliva flow rate.[190]

Central to the diagnosis of Sjögren's syndrome is the histopathological detection of pathognomonic features within salivary gland tissue. This comprises an infiltrate of mononuclear lymphocytes and other cells of chronic inflammation that are scored as foci of 50 lymphocytes, plasma cells and macrophages (focus lymphadenitis). A focus score of number of foci per 4 mm^2 is determined and for Sjögren's syndrome this must be greater than 1. In addition, unlike IgG4 disease, germinal centres are present in Sjögren's syndrome; indeed, it has been suggested that the presence of germinal centres may be a predictor of non-Hodgkin lymphoma development later in life.[185] As expected there is loss of salivary acini and peri-ductal fibrosis. Histopathological studies are typically performed on labial gland biopsy (LGB) tissue but as might be expected there can be considerable variation in the diagnosis of Sjögren's syndrome by histopathologists from different specialties and centres across the globe.

The classification system(s) may not always be helpful but Sjögren's syndrome is the likely diagnosis when a middle-to-late aged female has signs of ocular and oral dryness, is not on medication or has systemic disease likely to give rise to such a clinical picture and there are some radiological, serological and/or histopathological features suggestive of

such a process. In these circumstances, it would seem to be medicolegally sound to indicate that, while there is a risk that the disease is not Sjögren's syndrome, there is sufficient evidence to warrant the patient and attending clinicians being aware of the possible risk of lymphoma.

TREATMENT

Salivary substitutes

A number of synthetic salivary substitutes are available for the management of xerostomia, a number of them supplemented with calcium, phosphate and fluoride ions in order to prevent demineralization. However, since none of them can completely comply with the highly complex nature of saliva molecules, patients find them generally unsatisfactory – unless the xerostomia is mild. As a consequence of the variable effectiveness of these agents and sometimes their high financial cost to patients, many affected individuals resort to simply sipping water regularly.[189, 190] Moreover, as stated in a comprehensive review by Furness et al,[176] there is no conclusive evidence about their effectiveness for caries prevention.

Chewing gum

Salivary stimulation with sugar-free chewing gum may enhance salivary flow, increasing pH and buffer capacity.[191] The addition of substances such as polyols and carbamide apparently does not improve the caries-preventive effect of the chewing process itself.[192] However, these actions are likely to be transient, and full-denture wearers may be unable to use them – even when the manufacturers state that these agents are suitable for them.[193]

SYSTEMIC AGENTS

Sialagogues

Two muscarinic acetylcholine receptor agonists (pilocarpine and cevimeline) are licensed for the treatment of dry mouth symptoms due to Sjögren's syndrome. These agents stimulate the muscarinic acetylcholine receptors M1 and M3 present on salivary glands, leading to increased secretory function. No study has compared the efficacy and safety of these two drugs.

The clinical benefit of orally administered pilocarpine has been reported in large randomized, placebo-controlled clinical trials. A dosage of 5 mg pilocarpine four times daily resulted in increased whole saliva flow and improved dry mouth, dry eyes, nasal, vaginal and skin dryness.[194–196]

Pilocarpine therapy can also reduce the frequency of oral and ocular symptoms related to xerostomia and xerophthalmia. Data from RCTs have revealed a high frequency of adverse events associated with pilocarpine use, including sweating, increased urinary frequency and flushing (observed in 43%, 10% and 10% of patients, respectively).[197] These data suggest that pilocarpine may be of benefit in the symptomatic management of Sjögren's syndrome, but studies have not included patients with absolute xerostomia, who may have the most severe oral symptoms of long-standing oral dryness.[198]

Several double-blind studies confirmed that cevimeline significantly reduces symptoms of xerostomia and dry eyes in patients with Sjögren's syndrome.[199] The best results in RCTs were achieved with a dose of 30 mg/8 h.[200] The adverse effects of cevimeline mirror those of pilocarpine, with increased gastrointestinal symptoms and rigor but reduced urinary frequency in the case of cevimeline.[201]

Bethanechol, which has both muscarinic and nicotinic agonist actions, was suggested to be of potential use in the management of drug-induced xerostomia, but had never been objectively assessed.[202, 203]

Available data, including that of a placebo-controlled study,[204] suggest that the cholinesterase inhibitor pyridostygmine may be of benefit in the treatment of drug-related xerostomia, although there are no data on the efficacy of this agent in the management of other common disorders giving rise to xerostomia.

Bromhexine (32–48 mg daily) may increase salivary and lacrimal flow in patients with Sjögren's syndrome;[205, 206] however, there are little published data on the precise oral benefits of this therapy other than those of one study and the results of an animal study that suggested that bromhexine does not significantly alter the development or severity of Sjögren's syndrome-like disease.[207]

Biological therapies

Several studies have analyzed the use of biological agents in primary Sjögren's syndrome, including interferon alpha (IFN-a), anti-TNF (tumour necrosis factor) agents and B-cell targeting therapies.

Open label studies suggested that intramuscular (e.g. 1×10^6 IU/week) and parenteral (3×10^6 three times weekly) IFN-a increase the lacrimal and salivary flow of patients with primary and secondary Sjögren's syndrome.[208] Subsequent open and single blinded studies also suggested that IFN-a-containing lozenges (150 IU IFN-a 3 times daily) might reduce the severity of xerostomia in primary and secondary Sjögren's syndrome, clinical benefit being observed in some patients after 9 weeks therapy.[209, 210] Despite the promising results of these preliminary studies, a large RCT – including 497 of the 569 patients treated with IFN-a to date – observed that therapy with IFN-a tended to improve only unstimulated salivary flow and was associated with gastrointestinal adverse events.[211]

Two antiTNF agents, a monoclonal antibody against TNF (infliximab) and a recombinant soluble TNF receptor (etanercept) have been tested as potential therapy for primary Sjögren's syndrome. An openlabel study in 16 patients with Sjögren's syndrome demonstrated the efficacy of infliximab, based on subjective and objective measures.[212] However, the positive results were not confirmed in a subsequent RCT including 103 patients.[213] Etanercept, a recombinant soluble TNF receptor, has been tested in two small studies (one RCT, one prospective) revealing no significant difference in the main sicca characteristics and symptoms associated with Sjögren's syndrome after treatment.[214, 215]

As Sjögren's syndrome is characterized by B-cell hyperactivity, a large number of clinical trials investigated the efficacy of biologic agents with the B-cell depleting antibody rituximab. Two small placebo-controlled

RCTs comprising 47 patients demonstrated considerable improvements in sicca features, salivary flow rate, ocular tests results, fatigue and quality of life scores after treatment with rituximab.[216, 217] More than 10 uncontrolled trials found a reduction in extraglandular features in patients treated with rituximab, compared with placebo.[197] Two large double-blind studies have been undertaken in France and the UK to understand if rituximab can be used in large populations of patients with Sjögren's syndrome. The TRACTISS study in UK should be completed in mid-2014, whereas the results of the TEARS study have been recently published, indicating that rituximab infusions did not produce sustained or substantial alleviation of symptoms or improvement in disease activity in adults with recent-onset or systemic Sjögren's syndrome.[218]

Corticosteroids

While systemic corticosteroids may be beneficial for the management of accompanying connective tissue disorders, there are conflicting data of the precise benefits in reducing the oral or ocular symptoms of Sjögren's syndrome. The results of one randomized study suggested that prednisolone (30 mg on alternate days) was effective[219] in reducing dry mouth symptoms but failed to enhance salivary flow rate. Conversely increased salivary flow rate was demonstrated after corticosteroid irrigation of the major glands (e.g. with prednisolone 2 mg/ml saline).[220] The use of glucocorticoids in clinical practice in primary Sjögren's syndrome is not supported by reliable scientific evidence, since the available studies (all but one uncontrolled) have substantial methodological flaws in their design.[197] Additionally the use of systemic corticosteroids has been associated with a high rate of adverse events, including increased appetite and weight gain,[221] and a twofold higher frequency of diabetes mellitus compared with age-matched and gender-matched individuals without systemic autoimmune diseases.[222]

Antimalarials

Antimalarials such as chloroquine and hydroxychloroquine are widely used for treating Sjögren's syndrome. The main effect seems to be due to inhibition of the antigen-processing ability by macrophages and monocytes, leading to decreased production of interleukin-1 (IL-1), IL-6, TNF-a and interferon-g (IFN-g). Although no large RCTs exist to date, hydroxychloroquine may improve salivary functions by inhibition of glandular cholinesterase with a benefit sustained after 3–9 months of hydroxychloroquine use as reported in a retrospective study.[223–226]

Immunosuppressive agents

The immunosuppressive agents tested in Sjögren's syndrome are cyclophosphamide, azathioprine, methotrexate, leflunomide, mycophenolic acid and cyclosporine A. Unfortunately, present evidence suggests that these agents have limited benefits for sicca features and are associated with an unacceptable rate of adverse events (ranging between 41% and 100%).

The discovery of a soluble ligand of the TNF cytokine family, BAFF/BlyS (B lymphocyte stimulator), which is a prominent factor in B-cell differentiation, homeostasis, and selection, led to consideration of its use as a potential therapeutic target. Very recent data from a two-phase II open-label study on belimumab, a monoclonal anti- body targeting soluble BAFF, suggest this approach may have promise in primary Sjögren's syndrome[227] and further investigation is warranted.

Other strategies

It has been suggested that electrostimulation[228] and acupuncture[229] may increase salivary flow in some patients with Sjögren's syndrome, but good clinical evidence for such claim is lacking. Similarly the *in vivo* potential benefits of gene therapy (utilizing viral vectors of aquaporin) remain unknown. However, a recent study examining the distribution of AQP5 in the labial salivary gland cells concluded that salivary gland hypofunction in Sjögren's syndrome is probably not caused by reduced presence of AQP5.[230]

The results of one placebo-controlled investigation suggested that a herbally-based agent with vitamin supplements (LongoVital®) caused a prolonged increase in unstimulated salivary flow and reduction in Rose Bengal scores in a group of patients with Sjögren's syndrome. It has been suggested that evening primrose oil, rich in fatty acids important in inhibiting 2-series prostaglandins, may enhance salivary flow in some patients with Sjögren's syndrome.[231]

KEY POINTS

Head and neck manifestations of Sjögren's syndrome include:

- xerostomia, which can be profound, giving rise to dysarthria, dysphagia, increased frequency of caries and acute gingivitis but not periodontitis per se
- increased liability to candidal infection – notably acute pseudomembranous candidosis, and median rhomboid glossitis, chronic atrophic candidosis (denture-associated stomatitis) as well as angular cheilitis and acute suppurative parotitis
- dysgeusia and loss of taste – many affected people report most foodstuffs taste 'cardboard-like'
- intermittent swelling of the major salivary glands – notably the parotid glands; this often reflects non-specific inflammatory change within the glands
- solitary enlargement of a salivary gland, which may reflect chronic sialadenitis, acute suppurative parotitis and, importantly, non-Hodgkin lymphoma
- a possible 4% risk of non-Hodgkin lymphoma of major salivary glands.

BEST CLINICAL PRACTICE

- ✓ In treatment of xerostomia in Sjögren's syndrome, there is no evidence at present that systemic and immunologically active agents reduce the oral dryness of Sjögren's syndrome.
- ✓ Therapies such as electrostimulation may be promising therapeutic approaches in the future.

Chronic graft-versus-host disease

Allogeneic hematopoietic stem cell transplantation (allo-HSCT), the transfer of hematopoietic stem cells from one individual to another, is widely employed for the treatment of hematologic malignancies.[232] It has also been used to treat autoimmune or other non-malignant diseases such as immunodeficiency or haemoglobinopathies.[233, 234]

Chronic graft-versus-host disease (cGVHD) is the most important complication in long-term survivors after allogeneic hematopoietic stem cell transplantation, with nearly 50% of patients developing the disease.[235] Symptoms of cGVHD generally present within the first 3 years after HSCT and may affect only one organ or be widespread.[236]

Oral cGVHD can present as oral mucosal lesions (ulcers, lichen-type features and hyperkeratotic plaques) and salivary gland dysfunction. A reduction of the mouth opening due to the perioral deposition of collagen may also occur.[237, 238] The prevalence of oral mucosal lesions after allo-HSCT has been estimated to range between 45% and 83% among cGVHD patients.[239]

Salivary dysfunction of cGVHD has been documented since 1977,[240] and is characterized by Sjögren's syndrome-like manifestations, including hyposecretion of saliva and tears.[241] The early diagnosis of salivary gland dysfunction related to cGVHD is a key factor in the investigation of the cGVHD in other organs, since the clinical features of cGVHD often initially manifest in the mouth.[242]

A recent cross-sectional study revealed that xerostomia was reported by 77% of the patients with cGVHD.[238] Of note, just 27% of these patients had signs of hyposalivation. cGVHD affecting the salivary glands is characterized histopathologically by intralobular periductal lymphocytic infiltration (often with associated fibrosis) and exocytosis of lymphocytes into intralobular ducts and acini.[243] Immunohistochemical studies demonstrate a lymphocytic infiltrate of primarily CD41 and CD81 T lymphocytes as well as the presence of Langerhans cells and CD681 macrophages.[244] Sialochemical changes, with a reduction in the antioxidant capacity[245] and protein content, have also been observed.[246] Oral cGVHD may also be associated with recurrent superficial mucoceles, probably secondary to a damage to excretory salivary ducts.[247]

Patients affected by cGVHD have a higher risk of developing secondary solid tumours, in particular squamous cell carcinoma and salivary gland neoplasms. Kruse et al. reviewed the literature regarding the development of oral malignancy after HSCT over the last 30 years and found that cGVHD was present in 76.6% of cases before they developed the malignancy.[248]

Local therapy of cGVHD of salivary glands is aimed at stimulating the salivary flow with sialagogues and symptoms relief with salivary substitutes. Partially successful therapy is reported for pilocarpine,[249] which, however, can be problematic in patients with graft-versus-host disease involving the gastrointestinal tract for the increased secretion of gastric fluids.[250] It has been reported in a small case-series report that cevimeline treatment might improve xerostomia symptoms in patients with cGVHD.[251]

SOME SALIVARY GLAND SWELLINGS

Sialosis

Sialosis (sometimes termed sialoadenosis) is an uncommon non-neoplastic and non-inflammatory disorder giving rise to bilateral non-painful enlargement of the major salivary glands. Sialosis tends to arise in middle to late life with peak incidence in the 5th and 6th decades, although there have been reports of children being affected.[252, 253] There is a slight female predominance. The parotid glands are typically affected; indeed, often the enlargement is profound. The enlargement develops slowly and there may be some decrease in salivary flow, but xerostomia is not a common or dominant accompanying symptom.

The precise cause is unknown. The underlying pathogenesis is thought to reflect a neuropathy, in particular a neuropathy that results in dysregulation of autonomic control comprising a loss of parasympathetic activity and increased sympathetic drive, leading to an unopposed increase in protein content within the acinar cells.[254] This would thus explain the association of sialosis with diabetes mellitus and perhaps hypothyroidism, malnutrition, and alcoholic and other causes of hepatic cirrhosis. Sialosis has also been described in association with puberty and menopause, and as a reaction to antihypertensive medication. In diabetes mellitus the onset of sialosis seems to be unrelated to the duration or metabolic control of the endocrine disease.[254]

Salivary gland enlargement may affect up to 68% of individuals with bulimia nervosa. The aetiology of increased salivary gland size in bulimia nervosa remains unclear; however, it is suggested that binge eating may result in functional hypertrophy of the salivary glands. Alternatively, mild damage due to passage of fluid into the gland, autonomic neuropathy, endocrine disease or past alcohol use has also been suggested to cause this problem. Of note, a salivary gland enlargement may correlate with the frequency of bulimic symptoms and with levels of serum amylase. There presently remains no specific management for a salivary gland enlargement associated with bulimia nervosa; however, cessation of vomiting is generally associated with resolution of the parotid swelling.

Of interest, oral mucosal disease that affects the opening of Stenson's duct can give rise to painless swelling of one parotid gland, for example if a bulla forms around the opening. There is one report of a patient with pemphigus vulgaris developing recurrent bilateral non-suppurative parotid enlargement secondary to dehydration and possible mucus plug formation secondary to pemphigus vulgaris.[255] Sialosis is histopathologically characterized by acinar cell hypertrophy and atrophy of striated ducts associated with oedema of the interstitial connective tissue. Ultimately there is widespread fatty replacement of acini.

There is no defined therapy for sialosis. Management is typically directed towards correcting any underlying systemic disorder; however, sialosis associated with diabetes

mellitus, other endocrine disorders or hepatic cirrhosis is often resistant to treatment. Rarely, surgical reduction of parotid glands (e.g. superficial parotidectomy) may be required, although this clearly carries some risks. There remains one report of pilocarpine successfully resolving sialosis associated with bulimia nervosa.[256]

KEY POINTS

- Salivary gland enlargement due to sialosis may be associated with diabetes, hypothyroidism, malnutrition, hepatic cirrhosis, puberty, menopause and antihypertensive medication.
- Treatment is often difficult with endocrine and hepatic causes of sialosis being particularly resistant, even if the underlying disorder is addressed. Surgical reduction of the glands may be possible but should be a last-resort intervention

Pneumoparotitis (pneumosialadenitis, wind parotitis)

Pneumoparotitis is characterized by the presence of air within the parotid gland due to the reflux of pressurized air from the mouth into the parotid duct. The swelling may be unilateral or bilateral, and tender or non-tender. There may be crepitus and frothy saliva and air bubbles may emanate from the parotid duct during massage of the gland. The swelling of the parotid gland resolves over minutes to hours, although occasionally may take several days to resolve. Rarely, air may escape from the parotid gland giving rise to subcutaneous emphysema of the face and neck, mediastinum and possible pneumothorax.

Pneumoparotitis is most likely in people where raised intra-oral pressure is common – for example, wind instrumentalists, balloon and glass blowers. There are rare reports of pneumoparotitis secondary to bicycle tyre inflation, dental procedures using air powered equipment, cough associated with chronic obstructive airways disease, cystic fibrosis, whistling, nose blowing and the Valsalva manoeuvre to clear the ears. Occasionally pneumoparotitis may be self-induced, possibly reflecting mental illness. There have been reports of pneumoparotitis due to spirometry and, rarely, pneumoparotitis can arise without an identifiable cause.[257, 258] In most instances there is no associated infection (e.g. acute suppurative sialadenitis) or chronic sialadenitis, but both are possible.[259]

There is often no need for detailed investigation as the history is often suggestive of the cause. Sialography may demonstrate air bubbles within the duct and may also show sialectasis if repeated episodes of pneumoparotitis have resulted in infection and resultant sialadenitis. Ultrasound scanning can demonstrate similar features,[260] as may CT[261, 262] and, presumably, MRI.

Pneumoparotitis rarely warrants active treatment as there are few symptoms, the cause is usually easy to identify and there is a low risk of acute or chronic sialadenitis. Cessation of the factor causing the increase in intra-oral pressure results in generally complete resolution of signs but as this may interfere in the employment of musicians it is unlikely that many will follow this path. Pneumoparotitis is rare.

KEY POINTS

- Any persistent or significant rise in intra-oral pressure may cause pneumoparotitis.
- Management involves avoiding raised intra-oral pressures.

RANULA

Ranulas are cystic lesions that develop from extravasation of saliva, possibly following trauma to the sublingual gland or obstruction of the ducts.[263] The term ranula is the Latin word for a small frog, and it is used for the condition because it causes croaking speech and an oral ranula resembles a frog's belly. Ranulas have a prevalence of 0.2 cases per 1000 people.[264] Ranulas are connective tissue lined swelling of extravasated saliva. They usually manifest as a soft, blue-tinged swelling of the floor of mouth, are detected in the second decade of life and may have a female predisposition – although there are rare reports of ranulas in neonates that have required *ex utero* intrapartum treatment (EXIT). Lesions may be classified as simple (or intra-oral) when they lie above the mylohyoid, and deep or plunging when they invade below this muscle.[265] Plunging ranulas usually manifest as a painless persistent or recurrent neck swelling and, rarely, may spread to the upper chest wall. Respiratory obstruction secondary to a simple or plunging ranula is rare.[266]

A congenital predisposition to the development of plunging ranula has been suggested based on the observation of a larger number of ranulas in some ethnic groups and among siblings.[267] An increased occurrence of ranulas has been documented in HIV-infected individuals, which could be due to a blockage of the salivary gland by inflammation and peri-ductal fibrosis as part of HIV-associated salivary gland disease.[15]

Diagnostic confirmation typically necessitates radiological imaging appropriate for soft tissue swellings, possibly together with cytological examination of FNAB.[268]

Several surgical approaches and techniques for oral and plunging ranulas in paediatric and adult patients have been proposed, with a rate of success that ranges from 0% to 100%.[263] Among these, excision of the sublingual gland is associated with the lowest rate of recurrent disease, although it might give rise to several complications.[269] These include injury to the lingual nerve or Wharton duct, with possible stenosis, obstructive sialadenitis and ductal laceration. Bleeding and hematoma have also been observed following this procedure.[270]

A medical treatment for ranula based on the oral administration of nickel gluconate has been described and tested by Garofalo et al.[271] At low doses, nickel is thought to promote enzymatic functions and tissue-repairing process in salivary glands. The authors reported promising results in their case series, with no recurrence and lower incidence of side effects after medical treatment.[271]

HETEROTOPIC SALIVARY GLAND DISEASE

Heterotopic salivary gland disease is the presence of salivary gland tissue arising outside the normal distribution of the minor and major salivary glands (hence excludes accessory salivary gland tissue and salivary gland material associated with branchial cleft anomalies).[272] Heterotopic salivary gland tissue has been documented in the middle ear,[273] larynx,[274] lower neck,[275] chest wall,[276] sternoclavicular joint, and brain.[277] The exact mechanism of salivary gland heterotopia is uncertain, with a possible explanation being the entrapment of salivary tissue during embryogenesis or heteroplastic changes of epithelial tissue.[278] Generally these are asymptomatic incidental findings, although they can manifest as a mass or draining sinus.

Radiological imaging with or without histopathological examination of lesional tissue are the usual diagnostic procedures with complete surgical excision being the treatment of choice.[276] Neoplastic transformation of heterotopic salivary gland tissue is possible but rare.[279]

LYMPHOEPITHELIAL LESION

Lymphoepithelial lesion is an uncommon disorder that manifests itself as a recurrent or persistent swelling typically of the parotid gland. The submandibular gland may be affected in approximately 15% of individuals. Generally the swelling is non-painful.

Affected patients do not have clinical features of Sjögren's syndrome or features of other disorders likely to give rise to xerostomia, although they do have an increased risk of non-Hodgkin lymphoma. The histopathological diagnosis of BLEL is important as the clinical features mimic those of salivary gland malignancy, and histopathologically there can be some confusion with lymphomas. Surgical excision is the usual treatment of a BLEL.[280]

EXCESS SALIVATION (SIALORRHOEA)

Although excess salivation is uncommon, it can be distressing to both patients and carers. True excess salivation is extremely unusual, although it may sometimes arise following drug therapy. The majority of patients with excess salivation have difficulties in salivary control rather than hypersalivation.

There are no specific investigations for sialorrhoea, and the cause is often established from the clinical history.

There are few controlled studies of possible treatment for excess salivation. Young adults with likely long-term illness such as cerebral palsy may benefit from surgical relocation of the submandibular ducts together with removal of the sublingual glands. Likewise, the parotid ducts may be relocated to pass out in the tonsillar fossa.

Anticholinergic agents such as transdermal scopolamine or benztropine have been suggested to be of long-term benefit but more recently intra-glandular injection of botulin toxin has been found to be of application for the treatment of hypersalivation in adults[281, 282] and children[283] with a myotropic lateral sclerosis, cerebral palsy, Parkinson's disease and other causes of excess salivation.

A lower dose of RT (8–12.5 Gy) has been suggested to be effective for excess salivation of patients with amyotropic RT; indeed, in view of the often shortened lifespan of affected individuals, this may be a useful treatment for this disabling salivary disorder.

DROOLING

Drooling is the unintentional loss of saliva from the mouth,[284] common in normally developed babies but considered abnormal after age 4.[285] Drooling may arise as a consequence of impaired neuromuscular function, though less frequently it can be due to an increased production of saliva (idiopathic or drug-induced). In children, the most common cause of drooling is cerebral palsy, which persists in 37–58% of these individuals.[286, 287] In adults, drooling can be observed in 45% of patients affected by Parkinson's disease.[288] Neurological disorders also associated with drooling are cerebral palsy, amyotrophic lateral sclerosis and facial palsy.[289]

Drooling can give rise to a wide spectrum of clinical and functional complications such as impaired speech and eating, perioral skin breakdown, bad odour and infection. Aspiration-related and pulmonary complications are possible.[290]

Drooling is known to be difficult to treat. Management can be conservative or more invasive. Conservative treatments include changes in diet or habits, oral-motor exercises, intra-oral devices such as palatal training devices, and medical treatments such as botulinum toxin injections. More invasive treatments include surgery or radiation.

Behaviour modification to promote swallowing has been advocated for many decades but results are inconsistent, it requires motivation and is time-consuming.[291] Pharmacological therapy for drooling encompasses the use of anticholinergic agents, such as glycopyrrolate, benztropine andscopolamine to decrease saliva secretion through the parasympathetic autonomic nervous system. A systematic review investigated the efficacy of oral agents in the treatment of drooling concluding that, although effective, no one drug was preferable.[292]

Recently botulinum toxin, a neurotoxin that prevents the secretion of saliva by inhibiting the release of presynaptic acetylcholine, has emerged as a potential treatment for the management of drooling. The effectiveness of botulinum toxin has been reported in several clinical trials. A recent meta-analysis (2013) concluded that botulinum toxin decreases the severity of drooling with statistical significance in both adult and paediatric populations.[293] The duration of effect can vary from 6 weeks to 6 months.[294] However, there remains the need to establish the ideal dose and form of application. Botulinum toxin treatment may cause increased saliva thickness (3.9%), dysphagia (3.3%), xerostomia (dry mouth) (3.3%) and pneumonia (2.2%).[293]

Various surgical procedures have been suggested for treatment of drooling. These procedures all encompass an alteration in the anatomy of the salivary glands and include salivary gland excision, denervation of the salivary glands, and relocation or ligation of the salivary ducts.[295, 296] The most common surgical approach is the submandibular duct relocation. Ranula formation and submandibular duct obstruction have been reported in 8% of patients after submandibular duct relocation.[297] Resection of the major glands are not without their side effects, of course, the most frequent being xerostomia, visible scar and facial nerve weakness.[290, 298]

Radiation is rarely applied for the risk of xerostomia, loss of taste and development of malignancy of the approach.[299, 300] It is typically reserved for elderly patients who are not candidates for surgery and cannot tolerate medical therapies.[301]

KEY POINTS

- Sialorrhoea is uncommon.
- The common causes of drooling include cerebral palsy, amylotropic lateral sclerosis, traumatic brain injury, stroke and Parkinson's disease.
- Persistent drooling leads to angular cheilitis, excoriation of the lower facial skin and wetting of clothes.
- There are no specific investigations for sialorrhoea, the cause often being established from the clinical history.

BEST CLINICAL PRACTICE

- ✓ Young adults with likely long-term illness such as cerebral palsy may benefit from surgical relocation of the submandibular ducts together with removal of the sublingual glands. Likewise, the parotid ducts may be relocated to pass out in the tonsillar fossa.
- ✓ Intra-glandular injection of botulin toxin has been found to be of application for the treatment of hypersalivation in adults and children with amylotropic lateral sclerosis, cerebral palsy, Parkinson's disease and other causes of excess salivation.
- ✓ A low dose radiotherapy (8–12.5 Gy) is useful for patients with shortened lifespan and a disabling salivary disorder.
- ✓ Transdermal scopolamine or benztropine may be helpful

FREY'S SYNDROME (GUSTATORY SWEATING)

Frey's syndrome (FS), also called gustatory sweating or auriculotemporal syndrome, is reported as the most disturbing sequela in patients at more than 5 years after parotid surgery for benign disease.[302] It is characterized by facial warmth, flushing and sweating over the distribution of the auriculotemporal nerve and/or greater auricular nerve, stimulated by any gustatory stimulus.[303] The information found in the literature concerning the incidence of FS shows a great variation, ranging from 2.6%[304] up to 97.6%.[305] Rustemeyer et al.[302] reported that 23.5% of patients undergoing parotidectomy developed FS an average of 12 months after surgery, but only 44% of these patients were symptomatic. Gustatory sweating syndrome secondary to submandibular gland surgery or trauma is also possible, although they do not involve the auriculotemporal nerve.

The aetiology of FS is not entirely known. It is commonly explained as 'misdirected nervous regeneration'. During parotidectomy, the postganglionic parasympathetic fibres of the auriculotemporal nerve, which supplies the parotid gland, and sympathetic fibres supplying local sweat glands are sectioned. During the regeneration process, parasympathetic fibres may grow along the distal ends of sympathetic fibres to the skin vessels and sweat glands. Thus, a gustatory stimulus produces sweating accompanied by flushing and heating.[306, 307] The time necessary to regenerate the postganglionic parasympathetic nerve fibres could explain the latent period between intra-operative facial nerve injury and the onset of FS; in most reports, this interval has ranged from 5 weeks to several months after parotid gland surgery, but unusual cases have presented many decades (30 years) after surgery.[308]

Although this syndrome has been reported primarily after parotid gland surgery,[309] it has also been observed after temporomandibular joint trauma or surgery[303, 310, 311] and carotid endarterectomy.[312] In childhood it can be a complication of forceps injury, frequently misdiagnosed as food allergy.[313]

Minor's starch iodine test, allowing visual confirmation of the blue-black reaction in the sweating area, is thought to be the gold standard of diagnosis.[314]

Many patients with FS do not wish any therapy.[315] Currently, the most effective treatment is the subcutaneous infiltration of botulinum toxin A in the affected area, with a benefit lasting for 1.5 years for 60% of the patients.[316]

Data concerning the efficacy of prevention strategies for FS remain inconclusive. A systematic review concerning the effectiveness of the a surgical approach (sternocleidomastoid muscle flap) to prevent FS after parotidectomy suggests that total prevention is unlikely to be achieved with any technique because FS is found, to some degree, in all treated sample groups.[317]

KEY POINTS

- Gustatory sweating syndrome is a rare sequela of salivary gland surgery.
- Gustatory sweating syndrome presents as facial warmth, flushing and sweating over the distribution of the auriculotemporal nerve following a gustatory stimulus.
- Botulinum toxin injection may be helpful if treatment is needed.

SOME MINOR SALIVARY GLAND DISORDERS

Mucoceles

Mucoceles are probably the most common disorder of the minor salivary glands, typically presenting as single blue or translucent sessile swellings on the lower lip.

Mucoceles occur in both genders and in all age groups, the peak age of incidence being between 10 and 29 years. They are rare in infants, although can occur in neonates.

The lateral aspect of the lower lip is the most common site of recurrence of mucoceles, but other common sites include the floor of mouth and the ventral surface of the tongue. The usual clinical presentation is of a single, recurrent, fluctuant, painless, well circumscribed bluish swelling that ruptures easily to release viscid salty mucus. Occasionally mucoceles can be multiple or develop suddenly at mealtimes.

The majority of mucoceles are the extravasation type, in which duct damage causes pooling of mucus in the adjacent connective tissue. Retention mucoceles, the less common variant, arise after partial or complete obstruction of the excretory duct (e.g. a sialolith – although rarely clinically or histopathologically detected) leading to retention of glandular secretions and dilation of the duct. Extravasation mucoceles may be more frequent in young patients, whereas retention mucoceles may occur most often in middle to late life.

Some mucoceles may resolve spontaneously but large, recurrent or unsightly mucoceles often require to be surgically excised, or removed by laser or cryotherapy. Other therapies of less well proven efficacy include intralesional corticosteroid injections and gamma-linolenic (oil of evening primrose).[318]

Subacute necrotizing sialadenitis

Subacute necrotizing sialadenitis (SANS) is a rare non-specific inflammatory disorder of adults of unknown aetiology affecting the minor salivary glands. It presents as a rapid onset painful, non-ulcerated swelling of minor palatal salivary glands. Almost all reported affected patients have been male. SANS tends to be self-limiting, symptoms and signs resolving within 2 weeks, and is not associated with necrotizing sialometaplasia.[319–321]

Necrotizing sialometaplasia

Necrotizing sialometaplasia is an uncommon disorder that typically affects the minor salivary glands of the palate, although may rarely involve other minor salivary glands and, very unusually, the major salivary glands.[322] It presents typically as a palatal swelling that breaks down to give rise to localized, irregular ulceration.

Lesions can be large – up to 5 cm in diameter – and can give rise to local paraesthesia or anaesthesia; however, they generally heal within 4–90 days. Affected patients may have systemic features such as pyrexia, chills and malaise. Despite the sometimes extensive area of ulceration, bony involvement is rare. There have been rare reports of airway obstruction and excessive bleeding with hypovolaemia due to large areas of sialometaplasia.[323]

Necrotizing sialometaplasia is thought to arise from local ischaemia, possibly caused by direct trauma (e.g. from a denture or as part of an anorexia nervosa bulimia nervosa pattern),[324] placement of dental local anaesthetics, recreational cocaine use, RT, alcohol, tobacco smoking, upper respiratory tract infections, allergic disease, oral intubation and other surgical procedures, or sickle cell disease.

Of note, it may be clinically and histologically confused with malignancies such as a squamous cell carcinoma, mucoepidermoid carcinoma or non-Hodgkin lymphoma. Necrotizing sialometaplasia is characterized histopathologically by acinar necrosis with squamous metaplasia of the ductal epithelium. This latter feature underlies the possible diagnostic confusion between necrotizing sialometaplasia and squamous cell carcinoma.

Necrotizing sialometaplasia is usually self-limiting; however, in view of the possible clinical similarity between necrotizing sialometaplasia and oral malignancy, careful histopathological examination of biopsy material is essential. Any likely causative factors should be identified and removed.[325]

Cheilitis glandularis

Cheilitis glandularis (suppurative stomatitis glandularis) is a rare disorder that usually arises in adults (but can occur in children) manifesting as labial swelling and ulceration. The disease is localized almost exclusively to the lower lip, especially the contact zone between the lips, although there have been occasional reports of the condition affecting the upper lips and palate.[326] Affected individuals usually have swelling, eversion and protrusion of the lower lip secondary to inflammation of the minor labial salivary glands. The orifices of the minor salivary gland ducts are dilated and inflamed, and a mucopurulent secretion may be expelled from the ducts when the lip is compressed.

The precise aetiology remains unknown, although associations with syphilis and other more ill-defined bacterial infections, poor hygiene, tobacco use, actinic exposure and emotional disturbance have been suggested. A genetic predisposition has also been proposed but there are no substantial supportive data. The connection with actinic damage is perhaps supported by 6 of 22 affected patients in one series being albino.[327]

Cheilitis glandularis may be classified into three types based upon the severity of the disease – simplex, superficial suppurative and deep suppurative. The last two types represent a stage where there is bacterial infection, being clinically characterized by increased inflammation, suppuration and ulceration of the lip. The deep suppurative type has also been termed cheilitis apostematosa or myxadenitis labialis, while the superficial suppurative has also been termed Baelz's disease.

The histopathological findings are non-specific but include local chronic sialadenitis, mucous/oncocytic metaplasia and mucin in ducts. Dysplastic epithelial changes may occasionally occur, but although associated carcinoma of the lower lip has been reported, cheilitis glandularis is still considered to be a benign disorder that should be managed by conservative means.[326–328] There are no detailed randomized studies of the treatment and surgery; for example, vermilionectomy has been suggested to be effective. However, albeit rarely, mucoceles can occur following surgery.

The term suppurative stomatitis glandularis has also been suggested to describe cheilitis glandularis. Indeed, the terminology used in the previous relevant literature is confusing. Granulomatous cheilitis is unrelated to cheilitis glandularis, the former being a localized presentation of sarcoidosis, orofacial granulomatosis or Crohn's disease.[329]

Inclusion of salivary gland tissue

Cyst-like areas of radiolucency are seen in the region of the angle of the mandible. Such inclusions are also possibly the origin of rare intraosseous salivary gland tumours.[330]

FUTURE RESEARCH

There are many unknowns in the aetiology and treatment of non-neoplastic salivary gland disease. Perhaps the most relevant areas of investigation for the treatment of such disease remain:

- the establishment of the pathogenesis of HCV-related sialadenitis
- the determination of the aetiology of Sjögren's syndrome
- the development of strategies for the prevention and treatment of radiotherapy-induced salivary gland disease and, indeed, other causes of non-drug-related oral dryness.

KEY POINTS

- Non-neoplastic disease of the salivary glands is dominated by the symptom of oral dryness (xerostomia) and/or the sign of salivary gland enlargement.
- Oral dryness is typically caused by drug therapy or Sjögren's syndrome.
- Enlargement of one submandibular gland is likely to be sialolithiasis, while enlargement of one or both parotid gland(s) has a much wider range of non-malignant causes.
- While the investigation of salivary gland disease has advanced greatly there remains no reliably effective means of lessening oral dryness that is unrelated to drug therapy.

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CHAPTER 47

ANATOMY OF THE PHARYNX AND OESOPHAGUS

Joanna Matthan and Vinidh Paleri

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SEARCH STRATEGY

Data in this chapter are based on a PubMed search using the keywords: pharynx, nasopharynx, oropharynx, hypopharynx, laryngopharynx, constrictor, sphincter, elevator, oesophagus, adenoidectomy, tonsils, adenoids, Waldeyer's ring, soft palate, cervical oesophagus, thoracic oesophagus, abdominal oesophagus, Valsalva, tonsillectomy and post-tonsillectomy bleed.

ANATOMY OF THE PHARYNX

INTRODUCTION

Shaped like an inverted cone, the 12–14 cm long musculofascial tube that is the pharynx hangs down from the pharyngeal tubercle at the skull base and fuses with the oesophagus below at the level of the lower border of the cricoid cartilage. It is the continuation of the common pathway for respiration and digestion that begins with the oral cavity.

The pharynx acts as a single physiological structure in its role as the common aerodigestive pathway and its mucosal lining is shared with that of the auditory tubes, the nasal cavity, the oral cavity and the larynx. Functionally, in addition to directing air into the laryngeal inlet and food into the digestive tract, via the auditory tube, it also assists in the equalization of pressure within the middle ear and aids in vocalization of sound to facilitate speech.

An understanding of the anatomy of this region is vital to the otolaryngologist. Inflammatory and neoplastic diseases of the pharynx and oesophagus are common in the general population and form a substantial proportion of surgical work. With the advent of transoral surgery for pharyngeal cancers, in addition to the conventional knowledge of anatomy of this region, there is a need to appreciate the anatomy from 'inside out'.

SUBDIVISIONS OF THE PHARYNX

Anatomically, the pharynx is divided into distinctive subdivisions – the nasopharynx, the oropharynx and the hypopharynx (laryngopharynx) – the boundaries of which are purely arbitrary and based on their anterior communications with the respective nasal, oral and laryngeal cavities (**Figure 47.1**). Each of these subdivisions has a variety of structures within them of clinical relevance. The muscular wall and the layers of the wall, common to all the subdivisions, will be dealt with in separate sections.

Nasopharynx

The superior aspect of the pharynx, the region above the soft palate and behind the choanae, is the nasopharynx. This space has a roof, two lateral walls, a posterior wall and a floor, and it communicates with the oropharynx

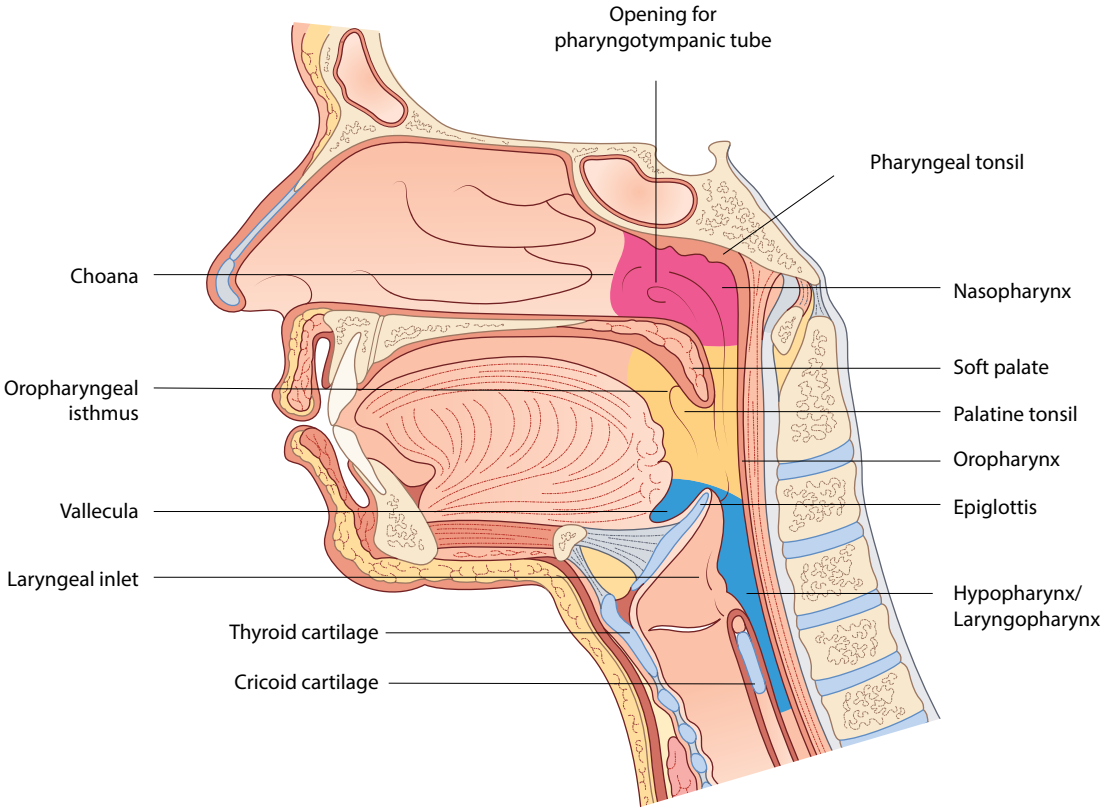


Figure 47.1 Sagittal section of the head and neck.

below via the pharyngeal isthmus posterior to the soft palate and anterior to the posterior pharyngeal wall. The important subsites within this space are the opening for the pharyngotympanic tube (also known as the auditory tube or the Eustachian tube), the pharyngeal recesses and the nasopharyngeal tonsils (or the adenoids).

The nasal cavity communicates posteriorly with this space and, thus, the anterior boundary of the nasopharynx is that formed by the right and left posterior nasal apertures, or the choanae, separated in the midline by the vomer, its bony septum. The posterior ends of the inferior and middle conchae from the lateral walls of the nasal cavity project medially into each choana. With the exception of the soft palate, the walls of the nasopharynx are rigid and the cavity thus always patent, allowing for unhindered flow of air, in sharp contrast to the cavities of the oropharynx and the laryngopharynx, which open and close on swallowing and with respiration.

The roof and posterior wall of the nasopharynx are contiguous due to the sloping nature of the inferior body of the sphenoid bone and the basilar part of the occipital bone, and it continues down to the level of the junction of the hard and soft palate. The bony deep structures within this region are often referred to as basisphenoid. Within the mucous membrane of the roof and posterior walls is a collection of lymphoid tissue known as the nasopharyngeal tonsil, maximal in size during childhood and contributing to the defence of the upper respiratory tract. Unlike oropharyngeal tonsillar tissue, there is no clear plane of cleavage in the nasopharyngeal tonsil, which makes excision less precise and complete during adenoidectomy (see **Boxes 47.1** and **47.2**).

The floor of the nasopharynx is formed by the soft palate (dealt with in detail below). The posterior and lateral walls of the nasopharynx are composed predominantly of the superior constrictor muscle and its overlying mucosa. Within the lateral wall sits the pharyngeal orifice of the pharyngotympanic tube, approximately 1–1.5 cm from the posterior end of the inferior turbinate at the level of the superior border of the palate – or the floor of the nose. This tube connecting the middle ear and the nasopharynx allows, by its transient opening and closing, the equalization of air pressure on both sides of the tympanic membrane. It is formed primarily by fibrous tissue and cartilage but also by bone, and it is more horizontal and approximately half its adult length at birth, allowing for easier spread of infection back and forth from the nasopharynx into the middle ear cavity in this age group. The orifice of this tube is covered with a cartilaginous projection, the torus tubaris, orientated posterosuperiorly, with the longer extension situated posteriorly and extending in a craniocaudal direction, which gives it its comma-shaped appearance. It also forms the anterior boundary of the pharyngeal recess, or fossa of Rosenmüller, situated posterosuperior to

BOX 47.1 Within the nasopharynx: the nasopharyngeal tonsils or adenoids

Size	Rapid growth during infancy, involutes during ages 8–10 and atrophies in later life. At its largest at age 5
Site	Roof and posterior wall of nasopharynx
Shape	Described as a truncated pyramid, with a vertically oriented median cleft, its apex directed towards the nasal septum and its base at the junction of the roof and posterior wall of the nasopharynx
Surface	Free surface has anteriorly and laterally radiating folds from the bursa of Luschka – a median blind recess or the pharyngeal bursa. This extends deep into the tonsil in a posterior and superior direction
Structure	Predominantly respiratory epithelium, ciliated in nature, on its lateral and inferior parts. Also contains occasional patches of keratinized stratified squamous epithelium. Anchored at its superior pole via a connective tissue hemicapsule onto which the tonsillar fibrous framework attaches
Supply	An anastomosis of the following arteries: ascending pharyngeal and ascending palatine arteries, tonsillar branch of facial artery, pharyngeal branch of maxillary artery and artery of pterygoid canal. Occasionally, an emissary vessel (off inferior hypophysial artery) to basisphenoid bone supplies the nasopharyngeal bed – a possible culprit in persistent haemorrhaging post adenoidectomy
Significance	Part of Waldeyer's ring of tonsillar tissue, contributing to the defence system of the upper respiratory tract
Surgical/clinical considerations	Inflammation of this tissue: **adenoiditis**, predominantly in children (peak age 5) when it causes persistent chronic otitis media infections, problems with nose breathing and intermittent sleep apnoea
	Adenoidectomy or the surgical removal of nasopharyngeal tonsils: blind curettage, suction diathermy or suction micro-debridement. During blind curettage, important to avoid hyperextending the cervical spine as arch of the atlas (cervical vertebra C1) may pierce through prevertebral fascia and cause infection and instability of the C-spine

the torus tubaris, which is the site of the tubal tonsils which, when present, constitute an additional component of Waldeyer's ring of tonsillar tissue (**Figure 47.2**). The superior constrictor and overlying mucosa forms its floor while the skull base forms the superior and posterior border. This fossa is the commonest site of the origin of nasopharyngeal carcinomas and should be targeted in biopsies of the nasopharynx in the context of carcinoma of the unknown primary. The fold of mucosa projecting inferiorly from the cartilaginous ridge of the pharyngotympanic orifice is the salpingopharyngeal fold, formed by overlying mucosa and the levator veli palatini and salpingopharyngeus muscles, the latter of which passes inferiorly and laterally to merge with the lateral pharyngeal wall.

Anteriorly, the epithelium of the nasopharyngeal wall is predominantly respiratory in nature, ciliated and pseudostratified, with goblet cells. More posteriorly, non-keratinized stratified squamous epithelium predominates and this continues into the oro- and laryngopharynx. At the point where the two types of epithelium meet – the transitional zone – instead of cilia, columnar epithelium with short microvilli are present, continuing superiorly to meet the nasal septum and laterally the pharyngotympanic tubal orifice towards the soft palate and lateral pharyngeal wall.

The sensory innervation of the nasopharynx is via the pharyngeal branch of the maxillary nerve, transmitted from the middle ear cavity via the pharyngotympanic tube. Posterior to the tubal orifice, the pharyngeal branch of the pterygopalatine ganglion supplies the majority of the mucosa. This branch passes through the palatovaginal canal along with a branch of the maxillary artery, its pharyngeal branch.

Oropharynx

The oropharynx continues caudally from the nasopharynx, connected to it via the pharyngeal isthmus. The boundary between the naso- and oropharynx is the start of the common aerodigestive tract and the site where the oral cavity, larynx and hypopharynx communicate. It therefore has dual functionality, coordinating breathing and swallowing. The space has anterior, lateral, posterior and superior walls and it communicates with the oral cavity via the oropharyngeal isthmus. The clinically relevant anatomical subsites within the oropharynx are the base of tongue and valleculae in the anterior wall, the palatine tonsils, the tonsillar fossae, the tonsillar (faucial) pillars and the glossotonsillar sulci in the lateral walls, and the inferior surface of the soft palate and the uvula in the superior part of the space. In addition to tonsillitis and peritonsillar abscesses within this region, the palatine tonsils and base of tongue are common sites of malignancy, in particular human papillomavirus-associated squamous cell carcinoma. Foreign bodies (typically, fish bones or food debris) may become lodged either in the palatine tonsils or in the valleculae.

The clinical boundaries of the oropharynx differ from those commonly indicated in anatomy textbooks as described above. It is bounded superiorly by a horizontal line drawn at the level of the hard palate, inferiorly by a horizontal line drawn through the floor of the valleculae and anteriorly by a vertical plane defined by anterior boundary of the palatoglossal folds (which contain the palatoglossus muscles and the overlying mucosa) to include the posterior third of the dorsum of the tongue. The posterior wall of the oropharynx is the extent of the posterior pharyngeal wall bounded by the imaginary lines drawn from the superior and inferior limits described above.

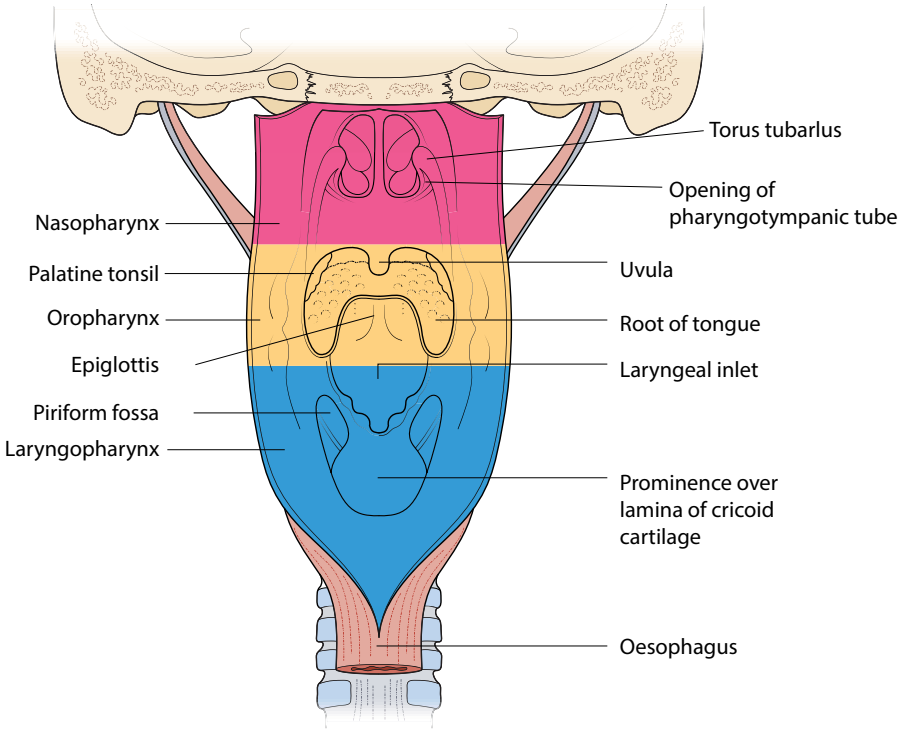


Figure 47.2 Features of the pharynx (posterior view with the pharyngeal wall opened).

The superior boundary of the oropharynx is the soft palate. This structure is suspended from the anterior bony projection of the palatine part of the hard palate and is essentially a mobile flap that opens and closes on swallowing. The point of demarcation between the soft and hard palates can be felt with ease and may demonstrate a change in colour, the soft palate possessing a yellowish discolouration on a base of a darker region than that of the anterior hard palate. Within the thick mucosal fold that is the soft palate, the soft palate muscles – five in total – and the thin and fibrous palatine aponeurosis, the neurovascular structures, the mucous glands and the lymphatics all lie in close proximity. All the soft palate muscles are attached to the palatine aponeurosis, which also encloses the small musculus uvulae muscle close to the midline. In the midline, the conical-shaped uvula containing the small musculus uvulae muscle forms the inferior free border and dangles down to extend into the oropharyngeal isthmus. The lateral aspects of the soft palate wall blend in with the lateral pharyngeal wall.

The lateral walls of the oropharynx have two prominent folds bilaterally, the faucial pillars. The anterior communication between the oral cavity and the oropharynx is via the oropharyngeal isthmus and is demarcated by the bilateral anterior palatoglossal arches, their underlying muscles and the horizontal intrinsic tongue musculature. Situated more posteriorly are the palatopharyngeal arches comprising the palatopharyngeus muscle and its overlying mucosal layer (**Figure 47.3**). Within the space between these two mucosal folds sit the palatine tonsils in the tonsillar fossae, the third component of Waldeyer's ring of lymphoid tissue.

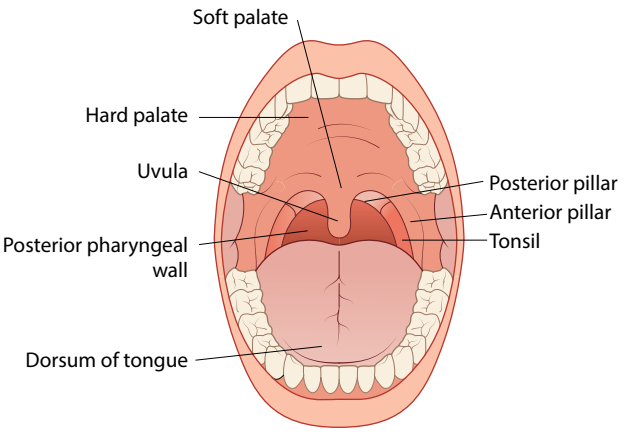


Figure 47.3 Oropharyngeal isthmus and tongue.

The posterior third of the dorsum of the tongue slopes downwards from the sulcus terminalis to form the anterior vallecular wall of the oropharynx (**Figure 47.4**). The nodular appearance of the mucous membrane in this region is largely due to the aggregations of lymphoid follicles – the lingual tonsils – which complete Waldeyer's ring. A midline ridge, or fold, of mucous membrane extending from the tongue to the anterior lingual surface of the epiglottis, the median glossoepiglottic fold, divides the valleculae into two shallow right and left depressions. Similar mucosal folds limit the valleculae laterally. These lateral glossoepiglottic folds extend from the lateral aspect of the epiglottis to the pharyngeal wall, not to the tongue as the name would suggest. These are sometimes referred to as the pharyngoepiglottic folds. The nerve supply in

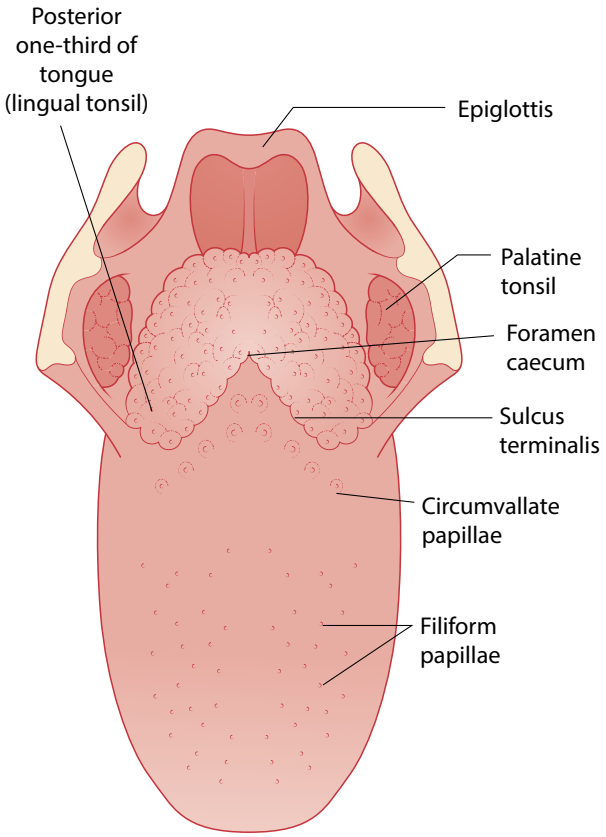


Figure 47.4 Anatomy of the tongue. The posterior third is part of the oropharynx.

this region of the oropharynx is via the internal laryngeal nerve, a branch of the vagus nerve. The mucosa in rest of the oropharynx is supplied predominantly by the glossopharyngeal nerve and to a lesser degree by the lesser palatine nerve.

PALATINE TONSILS

The palatine tonsils (**Box 47.2**) lie in the tonsillar fossa between two tonsillar pillars – the palatoglossal and the palatopharyngeal folds – and can be variable in the depth to which they are embedded between the folds. Previous infections, particularly peritonsillar abscesses, can cause apparent asymmetry of the palatine tonsils. True asymmetry is uncommon and should raise concerns about potential malignancy or parapharyngeal masses pushing the tonsil medially.

Palatine tonsils are characterized by multiple craters on their surface, which are formed by crypts passing deep into the parenchyma of the tonsil. The pitted epithelium of the tonsillar tissue has an intratonsillar cleft within the substance of the tonsil. Histologically unique, the palatine tonsils consist of lymphoid tissue covered by squamous epithelium. Unlike the other components of Waldeyer's ring, the palatine tonsil is encapsulated. This provides a convenient plane of dissection when performing tonsillectomy. The floor of the tonsillar bed is formed by the superior constrictor, and is separated from the tonsil by a thick condensation of pharyngeal submucosa, the tonsillar capsule, which is, in essence, an extension of the pharyngobasilar fascia. This capsule is further separated from the superior constrictor by a thin film of loose areolar tissue.

The palatine tonsils are supplied by the tonsillar artery, a branch of the facial artery that gains access to the tonsil by penetrating the superior constrictor to enter the inferior pole of the tonsil. There is additional arterial supply from the ascending palatine, lingual, descending palatine and ascending pharyngeal arteries. The venous drainage of the palatine tonsils is via a plexiform arrangement, deep to the tonsils, the pharyngeal venous plexus. The large external palatine vein descends from the soft palate and passes close to the lateral surface of the tonsillar capsule; this vein is most commonly divided in tonsillectomy and is the likely culprit in persistent post-tonsillectomy bleeds. The lymphatics of the tonsil drain to the jugulodigastric lymph node area.

The tonsils receive their nerve supply from the tonsillar plexus, a complex meshwork of nerves originating from the tonsillar branches of the maxillary nerve and the glossopharyngeal nerve. The fibres of the maxillary nerve are distributed to the lesser palatine nerves (although they pass through the pterygopalatine ganglion, they do not synapse there) and via these nerves are then combined with the glossopharyngeal nerve to form their plexiform arrangement of nerves around the tonsils. This plexus also supplies the oropharyngeal isthmus and the soft palate. An offshoot of the glossopharyngeal nerve, the tympanic nerve, also supplies the tympanic cavity and the tympanic membrane. Consequently, any pathology affecting the tonsils or the tonsillar fossa may present as pain referred to the ear.

WALDEYER'S RING

The pharynx in its nasopharyngeal and oropharyngeal part has a number of gut-associated lymphoid aggregates that make up what is known as Waldeyer's ring. This circumpharyngeal ring of mucosa-associated lymphoid tissue is at the entry point to the aerodigestive tract and its role almost certainly one of immune maturation and sampling. These include the adenoids posterosuperiorly, the superolateral tubal tonsils, anterolateral palatine tonsils and the anteroinferior lingual tonsils. The tubal tonsils are not always present. As well as these discrete aggregates, there are numerous areas of lymphoid tissue that are sited in the lamina propria just beneath the epithelium as well as collections of this tissue in the intertonsillar intervals. The former collections can often be seen on the posterior pharyngeal wall as small areas of salmon-pink, slightly raised swellings.

Hypopharynx

The hypopharynx (laryngopharynx, in anatomical textbooks) is the junction between the oropharynx and the oesophagus (**Figure 47.5**). Shaped like a funnel with much of its anterior segment missing, it extends from the level

BOX 47.2 Within the oropharynx: the palatine tonsils

Size	Varies according to age and pathological status – increase rapidly in size until ages 5–6 and at maximal size during puberty. Involution starts at puberty. Little lymphoid tissue exists in old age
Site	Within the lateral wall of the oropharynx, located between the palatoglossal and palatopharyngeal folds in the tonsillar bed, and surrounded by the tonsillar capsule
Shape	Ovoid mass of lymphoid tissue associated with the mucosa of the oropharynx and with a fixed position, long axis from superior to inferior to posterior
Surface	Free medial surface has a pitted appearance, with about 10–20 pits in total, which lead into blind-ending crypts that travel through the full thickness of the tonsils. The tonsils sit in a hemicapsule made up of connective tissue
Structure	Varies according to age and pathological status – they may be hypertrophied or inflamed, so difficult to say what is normal. Healthy tonsils have fissure-like crypts that are in contact with each other. The **recessus palatinus**, or **intratonsillar cleft**, is situated within the substance of the tonsil
Supply	Several anastomosing arteries but predominantly the tonsillar artery off the facial artery (a branch of the external carotid artery) Venous drainage is via the paratonsillar vein – external palatine vein – within the tonsillar hemicapsule, and via a plexiform venous drainage system outside the tonsillar hemicapsule Lymph drains to the jugulodigastric node of the deep cervical lymph node group
Sensation	The tonsillar branch of the glossopharyngeal nerve (CN IX) and the lesser palatine nerve (off the maxillary division of CN V2). Diffuse nerve supply
Service	The right and left tonsils are part of Waldeyer's ring of lymphoid tissue that provides first line defence to the upper respiratory tract
Surgical/clinical considerations	**Tonsillitis** refers to inflammation of the palatine tonsils. Pain can be referred to the middle ear due to innervation from different branches of the same cranial nerve (glossopharyngeal nerve). The tympanic branch of the glossopharyngeal nerve also supplies the middle ear, causing **referred pain** to the ear from the tonsils The internal carotid artery is 2.5 cm posterolateral to the tonsils A **peritonsillar abscess** or quinsy occurs outside the tonsillar capsule. Drainage is achieved by directly incising the most prominent bulging part of the collection, usually using topical anaesthetic spray **Tonsillectomy** or the surgical removal of the palatine tonsils: indications are recurrent acute infection of the tonsils, treatment for acute peritonsillar abscesses or for treatment of airway obstruction due to enlarged tonsils. Methods employed are the guillotine method or dissection in the plane of the fibrous hemicapsule, which is followed by electrocautery or ligation of the vessels. Usually performed under general anaesthetic but can be done using local anaesthetic infiltration of the region and/or nerve block. By separating the fibres of the superior constrictor muscle, the glossopharyngeal nerve can be accessed The paratonsillar vein (or external palatine vein) running within the tonsillar capsule is the usual culprit for a **post-tonsillectomy bleed**. This vein is commonly divided in a tonsillectomy

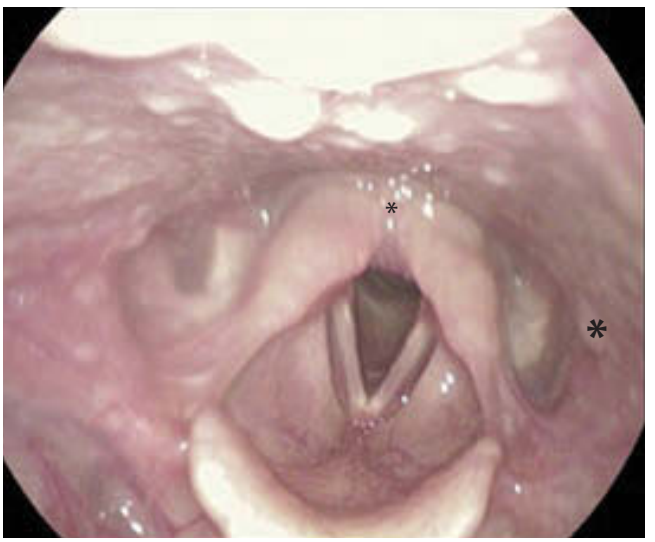


Figure 47.5 Endoscopic view of the hypopharynx during Valsalva manoeuvre allowing assessment of the upper postcricoid area (small asterisk – postcricoid area; large asterisk – pyriform sinus).

of the hyoid bone (or the superior margin of the epiglottis, delineated on either side by the lateral glossoepiglottic folds of the vallecular walls) to the lower margin of the cricoid cartilage at vertebral level C6 where the pharynx terminates and the oesophagus begins. The missing anterior segment corresponding to the laryngeal inlet, the aditus, is the communication between the larynx and the pharynx. This oblique area is bounded superiorly by the epiglottis, the posterior surfaces of the arytenoids and the cricoid cartilage inferiorly and laterally by the aryepiglottic folds. The mucosa in the hypopharynx is predominantly stratified squamous epithelium with goblet cells. Clinically, this region is often demarcated by imaginary lines: a horizontal line drawn posteriorly at the level of the cranial border the hyoid bone divides the hypopharynx from the oropharynx above and a horizontal line at the level of the caudal boundary of the cricoid cartilage indicates the start of the cervical esophagus below.

In its key position behind and to either side of the larynx, the hypopharynx is the crucial area in maintaining a

safe swallow and preventing aspiration of fluids and food boluses. It is made up of a number of subsites according to the International Union against Cancer (UICC) TNM (see Chapter 4, Staging of head and neck cancer) classification and tumours in this region have a poor prognosis due to their vague symptoms and the tendency to enlarge and metastasize prior to detection.

- The **posterior pharyngeal wall** extends from the horizontal line drawn at the level of the superior margin of the hyoid bone (or floor of the valleculae) to the level of the inferior border of the cricoid cartilage, and from the apex of one piriform recess to the other. Three overlapping constrictors form the posterior wall of the laryngopharynx to the level of the vocal cords. Beyond this point, the inferior constrictor is the main component of the wall behind the cricoid lamina and to the level of the upper margin of the cricoid cartilage. As the inferior constrictor is in reality composed of two separate muscles –thyropharyngeus and cricopharyngeus –this fusion point of these muscles, Killian's dehiscence, is a site of potential weakness and the site of pharyngeal pouches. This is discussed in more detail in 'Pharyngeal muscles' below.
- The bilateral **piriform recesses** or fossae extend from either side of the epiglottis from the lateral glossoepiglottic folds to the upper end of the oesophagus. They are broader superiorly and narrower inferiorly, and lie on either side of the laryngeal inlet. The recesses are formed by the larynx bulging into this part of the pharynx, leaving the bilateral anterolateral recesses. They are lined with mucosa and bounded medially by the quadrangular membrane of the larynx. The lateral boundaries are the thyrohyoid membrane superiorly and the thyroid cartilage inferiorly. Foreign objects commonly lodge in the recesses, and tumours can silently expand within the space asymptomatically until metastatic lymphadenopathy manifests.
- The pharyngo-oesophageal junction, or **postcricoid area**, fills out the rest of the hypopharynx. It extends from the level of the arytenoid cartilages and connecting folds to the inferior border or lamina of the cricoid cartilage, thus forming the anterior wall of the hypopharynx. The corresponding mucosa and submucosa extend from the inferior aspect of the arytenoids to the lower margin of the cricoid cartilage, and the lateral margins merge with the medial wall of the piriform recesses at the level at which the cricoid cartilage makes an anterior bend.

PHARYNGEAL WALL

The pharyngeal wall is composed of five discrete layers, two of which are fascial layers. The five layers, from deep to superficial, are the mucous membrane, submucosa, pharyngobasilar fascia, muscular layer and buccopharyngeal fascia or loose areolar sheath.

Mucosal layer

The mucosa of the nasopharynx is typical respiratory mucosa and is made up of ciliated, pseudostratified columnar epithelium. The rest of the pharynx is lined by non-keratinized stratified squamous epithelium. This change occurs at the transitional zone at the lower end of the nasopharynx.

Submucosal layer

Beneath the mucosa is a layer of submucosa, also termed lamina propria, which is made of connective tissue containing elastic tissue. In addition to the mucosal layer, it is host to a number of aggregates of gut-associated lymphoid tissue that forms Waldeyer's ring. The submucosa is thick and blends in with the fibrous pharyngobasilar layer, which also forms the tonsillar capsule.

Pharyngobasilar fascial layer

The pharyngobasilar fascia is the next layer and is firmly adherent to the skull base in the region of the occipital bone and petrous temporal bone. Superiorly, the fascia is thicker and fuses with the buccopharyngeal fascia to form a dense fibrous structure that suspends the pharynx from the base of skull. The muscular wall does not fully reach the skull base and this fascial layer is important in maintaining the integrity of the pharynx.

Muscular layer

The muscular layer is made up of three pharyngeal constrictor muscles that interlock like three cones or flowerpots one inside the other, with each layer overlapping the next layer. Their anterior aspects communicate with the spaces immediately in front of them, the nasal, oral and laryngeal cavities. The constrictor muscles have bilateral anterior attachments to the aforementioned cavities and sweep backwards from there to fuse on the posterior aspect of the pharynx at a midline raphe, the pharyngeal raphe. The muscular framework of the pharynx is dealt with in more detail below.

Buccopharyngeal fascial layer or loose areolar sheath

The final layer of the pharynx is a thin areolar layer covering the pharyngeal constrictors that is also continuous with the covering of the buccinator muscle. This layer contains the pharyngeal plexus of veins and nerves.

MUSCLES OF THE PHARYNX AND SOFT PALATE

The muscles of the soft palate and pharynx work in unison and are therefore dealt with together here.

Pharyngeal muscles

The pharyngeal muscular wall (**Figure 47.6**) is relatively thin and comprises three circular constrictor muscles, all of which act to enable the reflex of swallowing to ensure prompt propulsion of the food bolus by a coordinated peristaltic wave into the oesophagus. They are assisted by three longitudinal muscles, which act as elevators and dilators of the pharynx. The constrictors sit within each other like three stacked cones or cups and overlap on their posterior aspect. Although the framework of the pharynx dangles down from the base of the skull, and from the pharyngeal tubercle in particular, the muscular wall does not originate from the bony skull. Instead, the fibrous submucosal thickening of the pharyngeal wall, the pharyngobasilar fascia, stretches across like a curved but rigid sheet attached to the nasopharyngeal wall and fills the gap between the superior constrictor muscle below and the base of the skull above. In effect, the pharyngobasilar fascia is the fourth cone or cup stacked into the muscular constrictors below and is the main component for maintaining the patency of the nasopharynx in its task of guaranteeing unhindered flow of air for breathing.

All of the constrictors are supplied by the pharyngeal and superior laryngeal branches of the vagus nerve through the pharyngeal plexus.

THE THREE CONSTRICTORS

The superior constrictor is the thinnest of the constrictors and shaped like a quadrilateral sheet slung from one side of the pharynx to the other to form the superior part of the pharyngeal wall. Its function is to constrict the upper region of the pharynx. It arises from the pterygoid hamulus (but occasionally also from the posterior surface of the medial pterygoid plate) and the pterygomandibular raphe running from the pterygoid hamulus to the retromolar trigone, and from the posterior end of the mylohyoid line on the mandible. A few of its fibres originate from the side of the tongue. The pterygomandibular raphe is the fibrous condensation that extends between the buccinator and the superior constrictor muscles. The muscle fibres of the latter run backwards and upwards from their anterior attachments to fuse in the midline on the posterior aspect of the pharynx at the median pharyngeal raphe. Some fibres project upwards and attach to the base of the skull indirectly via the pharyngobasilar fascia, which attaches to the pharyngeal tubercle, a bony projection just anterior to foramen magnum. Posteriorly, the lowermost fibres sit comfortably within the overlapping middle constrictor muscle and reach the level of the laryngeal vocal folds. On the lateral aspect, the superior and middle constrictors do not overlap and a gap exists through which the stylopharyngeus muscle passes downwards to insert into the pharyngeal wall. Through the same gap, the styloglossus muscle as well as two nerves – the glossopharyngeal and the lingual – pass forwards in the direction of the tongue.

The fan-shaped **middle constrictor** arises from the inferior end of the stylohyoid ligament and the greater and lesser horns of the hyoid bone and its fibres fan out in several directions. Most of its fibres wrap around in the same manner as the superior constrictor fibres to join the median pharyngeal raphe while the upper fibres also encircle the lower posterior fibres of the superior constrictor. The lowest fibres of the middle constrictor muscle that angulate downwards in a dorsoventral direction also terminate at the level of the laryngeal vocal cords, along with those of the superior constrictor. The muscular anterior wall here is incomplete between the middle and the inferior constrictors and is covered by the thyrohyoid membrane, which forms part of the anterior wall in the hypopharynx. On the superolateral aspect of this membrane, the internal laryngeal nerve and the superior laryngeal artery and vein pass medially.

The inferior constrictor, the thickest of all the constrictors, is generally described as two muscles, the thyropharyngeus and the cricopharyngeus. Thyropharyngeus originates from the oblique line of the thyroid lamina,

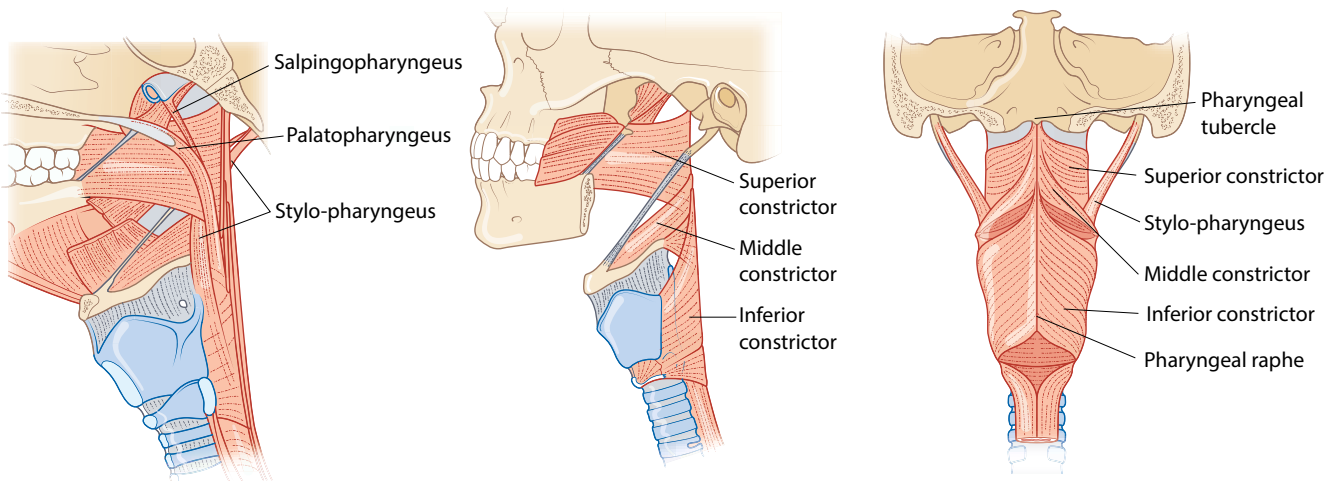


Figure 47.6 Muscles of the pharynx: (a) sagittal section, **(b)** lateral view and **(c)** posterior view.

from a small strip of lamina behind it and a small part of the inferior thyroid horn as well as from a part of the tendinous fascia overlying and looping over the cricothyroid muscle. Its fibres pass upwards posteromedially to join at the median pharyngeal raphe, although some of its fibres cross over the raphe to fuse with the contralateral muscle. Its upper fibres overlap with the middle constrictor fibres. Cricopharyngeus arises from the lateral aspect of the cricoid cartilage, emerging from between the attachment for the cricothyroid muscle and the inferior thyroid horn. It is distinctively different from all the other flat constrictor muscles in that it is thicker and rounder and its fibres pass horizontally to encircle the cricoid arch without fusing in the midline at the pharyngeal raphe. This is the sphincter of the pharynx, which is also continuous with the circular muscular coat of the upper oesophagus below. By default, this sphincter is closed and only opens momentarily during swallowing, and it can thus pose problems when passing an endoscope past this point. Swallowing will overcome any resistance encountered.

The innervation, attachments and functions of the three constrictor muscles of the pharynx are summarized in **Table 47.1**. The attachments are illustrated in **Figure 47.7**.

The inferior laryngeal artery and vein as well as the recurrent laryngeal nerve pass upwards deep to the inferior constrictor's lower margin.

The potentially weak area at the junction of thyropharyngeus and cricopharyngeus has clinical implications. The mucosa between these two muscles has little support from the pharyngeal musculature and is known as the pharyngeal dimple or, more commonly, Killian's dehiscence. The specific site of weakness is on the posterior aspect, in the midline, of the fusion point of these two muscles. This area is important in the pathogenesis of pharyngeal diverticulae, which form as a prolapse of mucosa and submucosa of the pharynx just above the cricopharyngeus muscle at the level of the sixth cervical vertebra. The resulting pharyngeal pouch (**Figure 47.8**) then becomes a convenient reservoir for trapping some or all of the passing food bolus. Halitosis and regurgitation are, unsurprisingly, the hallmarks of the condition. The specific aetiology of a pharyngeal pouch is, however, unknown. It is thought that malfunction of the upper oesophageal sphincter may contribute to the condition.

Despite the initial posterior expansion of any prolapse, prevertebral fascia prevents any further expansion in that direction. Thus, any larger prolapses usually project more laterally and inferiorly, mainly to the left side of the pharynx, which is the more exposed of the two sides. In a progressively enlarging prolapse, the pouch can potentially push the oesophagus to one side and thus sit in line with the rest of the pharynx. Consequently, dysphagia and cachexia may result, and pouch contents are more liable to spill into the larynx causing respiratory infections. The aetiology of the formation of a pharyngeal pouch is thought to involve a sequence of events originating from

TABLE 47.1 Constrictors of the pharynx

Muscle	Innervation	Anterior attachment	Posterior attachment	Function
Superior constrictor	Vagus nerve	Pterygomandibular raphe and adjacent bone on the mandible and pterygoid hamulus	Pharyngeal raphe	Constricts the pharynx
Middle constrictor	Vagus nerve	Greater horn of hyoid bone (upper margin) and adjacent margins on lesser horn of the hyoid bone and the stylohyoid ligament	Pharyngeal raphe	Constricts the pharynx
Inferior constrictor	Vagus nerve	Cricoid cartilage, oblique line of the thyroid cartilage, and the ligament that is between these two attachments and crosses the cricothyroid muscle	Pharyngeal raphe	Constricts the pharynx

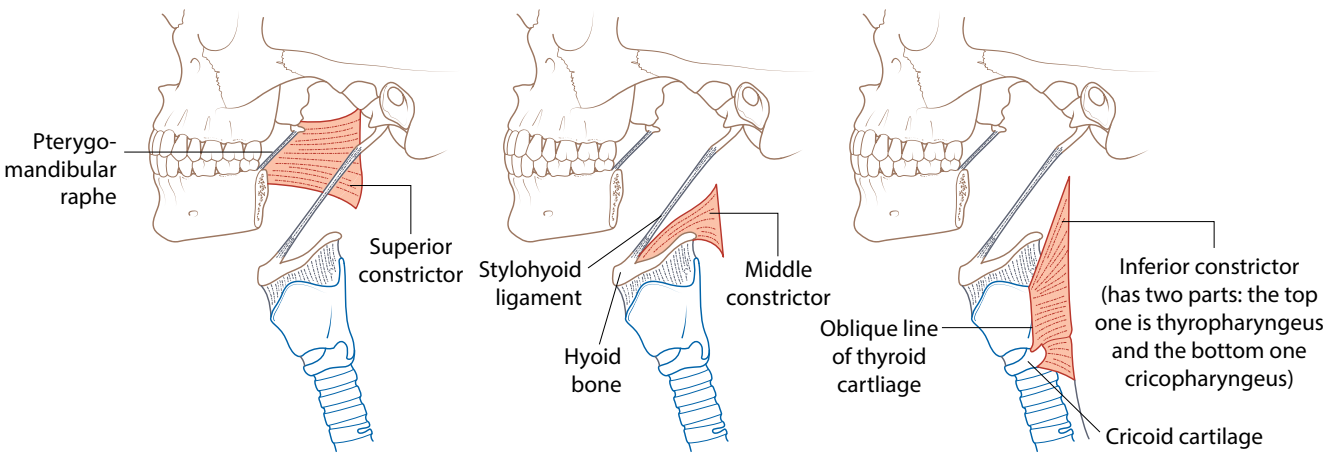


Figure 47.7 Attachments of the constrictor muscles of the pharynx: 1 – superior constrictor, 2 – middle constrictor, 3 – inferior constrictor.

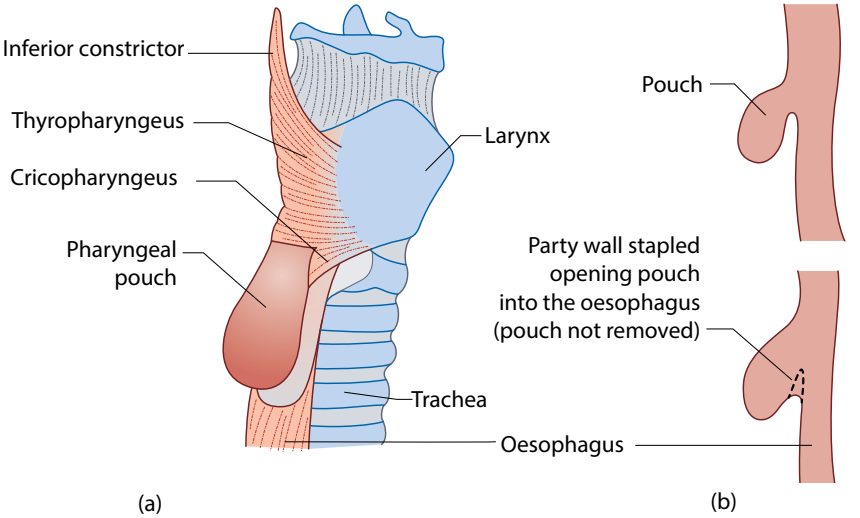


Figure 47.8 Anatomy of a pharyngeal pouch and stapling.

discoordinated swallow which elevates the pressure adjacent to the dehiscence and delays the relaxation of the cricopharyngeus sphincter below.

THE THREE DILATORS AND ELEVATORS

In addition to the three constrictor muscles that form the external muscular wall of the pharynx, three longitudinal muscles act to elevate and dilate the pharynx. These are the stylo-, palato- and salpingopharyngeus muscles. The first two are named based on their origins on the skull base; salpingopharyngeus, in contrast, has a long and slender shape with a wider distal end, the structure of which is reminiscent of the Greek trumpet bearing its name (salpinx).

The stylopharyngeus muscle is a long conical muscle that descends inferiorly between the external and internal carotid arteries. Curiously shaped, it is cylindrical above but flat below, and is markedly slender. It enters the pharynx between the superior and middle constrictors. It originates from the medial side of the base of the styloid process, within the temporal bone, and inserts into the posterosuperior border of the thyroid cartilage alongside the palatopharyngeus muscle. Some of its fibres also merge with the lateral glossoepiglottic folds, the lateral boundaries of the valleculae in the oropharynx. Its action is to raise the pharynx and assist in peristaltic movement of the food bolus. An important relation is the glossopharyngeal nerve which, en route to the tongue, curves from medial to lateral on its posteroinferior border and innervates it. All the other pharyngeal muscles are innervated by the pharyngeal nervous plexus, although cricopharyngeus is also innervated by the recurrent and external laryngeal nerves. Stylopharyngeus elevates both the pharynx and the larynx.

Palatopharyngeus is as much a pharyngeal muscle as it is a muscle of the soft palate. It has two heads and thus two actions. While both heads lie in the same plane, they are separated by levator veli palatini, a soft palate muscle. Its thicker anterior head originates from the posterior border of the hard palate and the anterior and superior surfaces of the palatine aponeurosis respectively. Its posterior head also originates from the superior surface of the palatine aponeurosis, but from further back on it. These two heads fuse at the lateral border of the palatine aponeurosis, are joined by fibres of salpingopharyngeus and arch downwards from here to insert into the posterior border of the thyroid lamina alongside stylopharyngeus and salpingopharyngeus. As it makes its way down as a single muscle covered in submucosa and mucosa, it forms the posterior faucial pillar, or palatopharyngeal arch. This muscle has a dual purpose: it elevates the larynx and pharynx and constricts the palatopharyngeal arch to assist in swallowing and, additionally, enables the concave shape of the oral surface of the palate with its arch.

The fibres of palatopharyngeus originating from the anterior head are horizontal at the level of the first cervical vertebra and form the palatopharyngeal sphincter. Contraction of these fibres lifts up the posterior pharyngeal wall in what is reminiscent of a ridge, Passavant's ridge, which is in direct contact with the superior surface of the soft palate during swallowing. No consensus has been reached on the origins of Passavant's ridge, some sources stating that it could be superior constrictor, and others that a completely different muscle acts as a sphincter at this point. What is clear is that there is a change of mucosal type along the line of this sphincter, from the ciliated, columnar respiratory epithelium above to the stratified squamous epithelium below.

Shaped like a long and slender trumpet, the salpingopharyngeus muscle arises from the lower part of the cartilaginous pharyngotympanic tube and descends internally in the salpingopharyngeal fold and inserts by blending into the palatopharyngeus muscle. The action of this muscle is to elevate the pharynx, although it may also serve to assist the soft palate muscle, tensor veli palatine, in opening the cartilaginous part of the pharyngotympanic tube during swallowing.

The innervation, origin, insertion and functions of the elevators of the pharynx are summarized in **Table 47.2**. Their attachments are illustrated in **Figure 47.9**.

Box 47.3 summarizes the openings in the pharyngeal wall musculature.

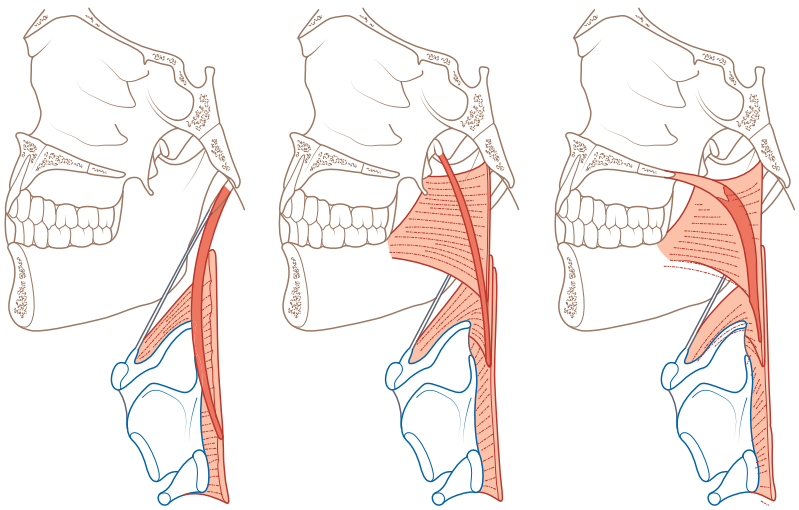
Soft palate muscles

Sloping down from the hard palate into the nasal and oral parts of the pharynx is the mobile flap which is the soft palate (**Figure 47.10**). It is the fibromuscular continuation of the hard palate and acts as a partition between the oropharynx and the nasopharynx. The failure of this structure and the consequences related to this are clearly seen in children born with a cleft palate, who struggle with feeding as well as normal speech production due to velopharyngeal incompetence.

The boundary between the soft and hard palate is easily palpable and is characterized by a subtle change in colour; the soft palate is characterized by a yellowish discolouration on a background of a darker red than that visible in the region of the hard palate. The soft palate is essentially a thick mucosal fold that holds within it an aponeurosis, muscles, neurovascular structures, lymph nodes and mucous glands. In its relaxed state, it is pendulant and a midline raphe is visible on its concave oral surface. The soft palate requires an intact central fibrous aponeurosis

TABLE 47.2 Elevators of the pharynx

Muscle	Innervation	Origin	Insertion	Function
Palatopharyngeus	Vagus nerve	Upper surface of palatine aponeurosis	Pharyngeal wall	Elevates the pharynx and closes the oropharyngeal isthmus
Stylopharyngeus	Glossopharyngeal nerve	Medial side of base of styloid process	Pharyngeal wall	Elevates the pharynx
Salpingopharyngeus	Vagus nerve	Inferior aspect of pharyngeal end of pharyngotympanic tube	Pharyngeal wall	Elevates the pharynx



1 Stylopharyngeus **2** Salpingopharyngeus **3** Palatopharyngeus

Figure 47.9 Attachments of the longitudinal muscles of the pharynx: 1 – stylopharyngeus, 2 – salpingopharyngeus, 3 – palatopharyngeus.

BOX 47.3 Openings in the pharyngeal wall musculature

Where?	Structures traversing
Above the superior constrictor	The cartilaginous portion of the pharyngotympanic tube, the tensor and levator palati muscles and the palatine branch of the ascending pharyngeal artery. All of these structures pass through the pharyngobasilar fascia
Between the superior and middle constrictor muscles	The stylopharyngeus muscle, styloglossus muscle, the glossopharyngeal and lingual nerves
Through the thyrohyoid membrane to enter the piriform fossa	The internal laryngeal nerve and superior laryngeal vessels
Below cricopharyngeus	The recurrent laryngeal nerve and inferior thyroid artery pass superiorly into the larynx deep to the cricopharyngeus muscle

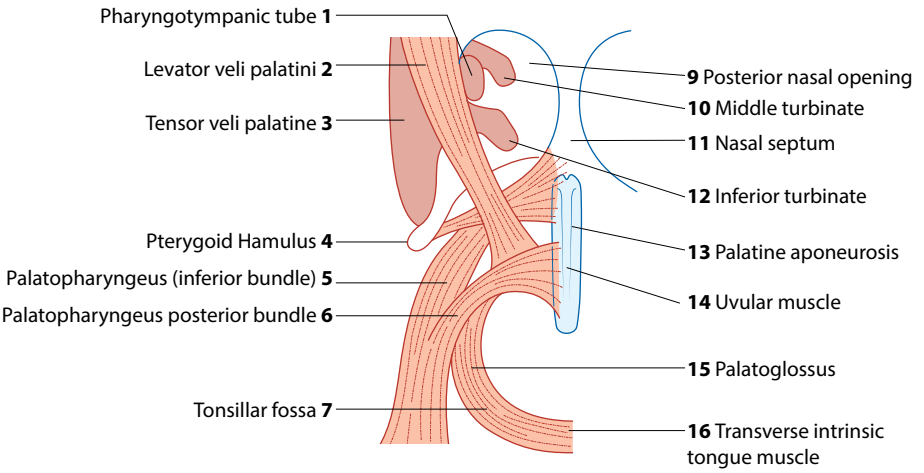


Figure 47.10 Posterior view of the soft palate showing the muscles acting on the left-hand side.

formed by the fused expanded tendons of the tensor veli palatini muscles upon which the muscles attached to the palate can act. The aponeurosis is attached posteriorly to the palatine part of the hard palate and has a midline raphe. The soft palate has a thicker anterosuperior portion near its insertion with the hard palate. As the palate travels posteroinferiorly, it gradually thins out, giving off the characteristic curved lower border appearance as it merges with the palatoglossal muscles which insert into it. In the centre is the conical uvula, part of its free inferior border, which can vary in length (but is typically longer in those who snore or have sleep apnoea) and projects downwards. The uvular muscles are embedded in the aponeurosis which splits to surround them. From the uvula, the two muscles of the pharyngeal arches – palatopharyngeus and palatoglossus – diverge laterally and inferiorly and insert into the intrinsic muscles of the tongue. The mucosa of the soft palate is covered in mucinous glands as well as minor salivary glands, and some taste buds exist on its oral surface.

The muscles of the palate do not act independently but work in unison to facilitate the swallowing reflex to close off the nasopharyngeal sphincter on initiating a swallow. All of the five paired soft palate muscles are attached to the palatine aponeurosis, the latter of which also encloses the small musculus uvulae muscle in the midline. These muscles can be classified according to their anatomical function: tensor veli palatini, levator veli palatini and the musculus uvulae raise the soft palate; palatoglossus (also an extrinsic tongue muscle) and palatopharyngeus (also a pharyngeal muscle) elevate the tongue and pharynx to close off the oropharyngeal isthmus during swallowing.

ELEVATORS OF THE SOFT PALATE

Tensor veli palatini is a veil-thin triangular muscle arising from the scaphoid fossa of the sphenoid bone, the lateral lamina of the pharyngotympanic tube and the spine of the sphenoid. It descends on the lateral surface of the medial pterygoid plate and then forms a tendon that hooks around the pterygoid hamulus to spread out to form the palatine aponeurosis. Its two sides fuse in the median raphe. Upon bilateral contraction, the muscles tauten predominantly the anterior part of the soft palate and depress the arch. Unilateral contraction of the muscles moves the soft palate in the direction of the pull. A primary function of the tensor veli palatini muscle is also presumed to be associated with opening the pharyngotympanic tube during swallowing and yawning to allow for equalization of nasopharyngeal and middle ear air pressure. This explains why patients with cleft palate will almost universally have otitis media with effusion; due to a failure of the midline connection, the tensor veli palatini cannot pull open the pharyngotympanic tube and, so, aeration of the middle ear as well as protecting it from the transmission of infections from the pharynx is negligible. The tensor veli palatini is the only muscle of the palate that is supplied by a branch of the mandibular division of the trigeminal nerve – the nerve to medial pterygoid. The rest are supplied by the cranial part of the accessory nerve via the pharyngeal plexus.

Levator veli palatini is a cylindrical muscle that arises from a small tendon on the inferior, roughened, portion of the petrous temporal bone, known as the quadrate area, situated in front of the inferior opening of the carotid canal. Some of its fibres also originate from the lower part of the cartilaginous pharyngotympanic tube and yet more from the vaginal process of the tympanic bone. It inserts onto the nasal surface of the palatine aponeurosis and sits between the two heads of the palatopharyngeus muscle, forming a rounded belly. The levator muscles pass anteromedially and together they form a V-shaped sling just above and behind the palatine aponeurosis, which allows elevation and slight retraction of the vertical posterior part of the soft palate when closure of the nasopharynx is required. The soft palate then touches the posterior pharyngeal wall, closing off the nasopharyngeal isthmus to prevent nasal regurgitation during speech and swallowing. Additionally, its fibres also pull the lateral nasopharyngeal wall anteromedially to narrow that space. The effects of levator veli palatini on the pharyngotympanic

tube and its role in the equalization of air pressure are controversial. This muscle, along with the palatoglossus, palatopharyngeus and uvular muscle, are all supplied by the cranial part of the accessory nerve via the pharyngeal plexus.

Musculus uvulae lies between the two laminae of the palatine aponeurosis and arises from the posterior nasal spine on the palatine bone as well as from the superior surface of the aponeurosis. It sits above the V-shaped sling formed by the two levator veli palatini muscles and runs backwards above it to insert into the uvular mucosa. Most of this small muscle is fused in the midline. Its function is to act in conjunction with the levator veli palatini muscles to retract and thicken the mid-third of the soft palate, thus closing the nasopharyngeal isthmus. As the two muscle bellies run at 90 degree angles to each other, when they contract, a 'levator eminence' is formed. This helps in the finally sealing off of the nasopharynx during swallowing.

ELEVATORS OF THE PHARYNX AND TONGUE

As a pharyngeal wall muscle, **palatopharyngeus** has been discussed in the section on pharyngeal muscles. Its role as a soft palate muscle is to elevate the pharynx and pull it forwards and medially. Additionally, the muscles acting together also draw the palatopharyngeal arches together and approximate them, enabling closure of the oropharyngeal isthmus.

Palatoglossus is both an extrinsic tongue muscle and a soft palate muscle. It arises from the palatine aponeurosis, on its oral surface, where it is continuous with the contralateral muscle, and projects anteriorly, inferiorly and laterally to the side of the tongue, forming the palatoglossal fold anterior to the palatine tonsil on its way down. A few of its fibres extend into the dorsum of the tongue, while others pass into the parenchyma of the tongue to intermingle with the intrinsic musculature. Unlike the rest of the extrinsic and intrinsic tongue muscles, palatoglossus follows the innervation of the soft palate muscles and is innervated by the cranial part of the accessory nerve and its pharyngeal plexus. Its action is to elevate the root of the tongue and to approximate the two palatoglossal arches when closure of the oropharyngeal isthmus is required.

The innervation, origin, insertion and functions of the elevators of the muscles of the soft palate are summarized in **Table 47.3**. Their attachments are illustrated in **Figure 47.11**.

BLOOD SUPPLY OF THE PHARYNX

The pharynx has a rich vascular supply from a number of branches of the external carotid artery. Much of the superior pharynx is supplied by the ascending pharyngeal artery. This artery arises from the medial external carotid and passes superiorly, giving off branches to the pharynx. A palatine branch passes over the edge of the superior constrictor to supply the soft palate and internal pharynx as well as the pharyngotympanic tube. There are additional supplies from the tonsillar artery and ascending palatine branch of the facial artery as well as, more inferiorly, from the superior and inferior laryngeal arteries.

Venous drainage is via the internal submucosal and the external pharyngeal venous plexus, which sits predominantly on the posterior aspect of the middle constrictor. The venous plexus drains into the internal jugular vein and, to an extent, connects with the pterygoid venous plexus. The venous plexus is a common cause of significant

TABLE 47.3 Muscles of the soft palate

Muscle	Innervation	Origin	Insertion	Function
Tensor veli palatini	V3, mandibular nerve via the branch to the medical pterygoid muscle	Scaphoid fossa of the sphenoid bone, fibrous part of the pharyngotympanic tube and the spine of the sphenoid	Palatine aponeurosis	Tenses the soft palate and opens the pharyngotympanic tube
Levator veli palatini	Vagus nerve via the pharyngeal branch to the pharyngeal plexus	Petrous part of the temporal bone anterior to the opening for the carotid canal	Superior surface of the palatine aponeurosis	The only muscle to elevate the soft palate from the neutral position
Palatopharyngeus	Vagus nerve via the pharyngeal branch to the pharyngeal plexus	Superior surface of the palatine aponeurosis	Pharyngeal wall	Depresses the soft palate, moves the palatopharyngeal arch towards the midline and elevates the pharynx
Palatoglossus	Vagus nerve via the pharyngeal branch to the pharyngeal plexus	Inferior surface of the palatine aponeurosis	Lateral margin of the tongue	Depresses the palate, moves the palatoglossal arch towards the midline and elevates the back of the tongue
Musculus uvulae	Vagus nerve via the pharyngeal branch to the pharyngeal plexus	Posterior nasal spine of the hard palate	Connective tissue of the uvula	Elevates and retracts the uvula and thickens the central region of the soft palate

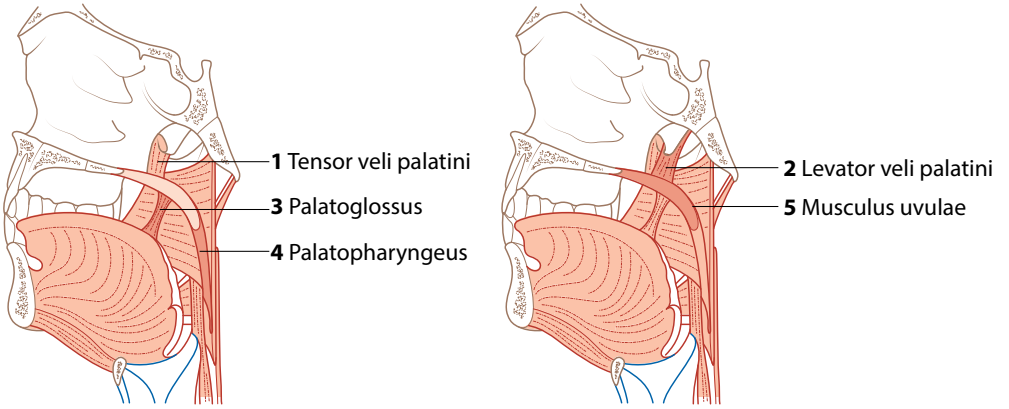


Figure 47.11 Soft palate muscular attachments.

bleeding in operations of the pharynx and can, on occasion, be very difficult to control.

The vascular supply of the soft palate is equally rich, but it mainly originates from the lesser palatine artery of the maxillary artery, and the ascending pharyngeal artery and its palatine branches in particular. These arteries form a complex anastomosis with the ascending palatine artery, a branch of the facial artery.

PHARYNGEAL PLEXUS OF NERVES

The motor and the majority of the sensory supply to both the pharynx and the soft palate come from the pharyngeal plexus. This is a meshwork of interconnecting nerves on the posterolateral surface of the pharynx and it is formed by contributions from the pharyngeal branches of the vagus nerves, the glossopharyngeal nerves and the sympathetic branches of the superior cervical ganglion. Mixed nerves then exit the plexus and either descend or ascend over the external surface of the pharyngeal constrictors, in particular over the middle constrictor, to supply the deeper layers of the pharyngeal wall, the muscles and the mucosal surfaces.

The motor fibres of the plexus originate in the cranial root of the accessory nerve and are carried by the pharyngeal branch of the vagus nerve to supply all of the pharyngeal muscles, apart from the stylopharyngeus muscle (which is supplied by the glossopharyngeal nerve) and the tensor veli palatini (which is supplied by nerve to medial pterygoid, a branch of the mandibular division of the trigeminal nerve). These motor fibres travel between the internal and external carotid arteries to enter the superior margin of the middle constrictor. At this point, it joins the hypoglossal nerve – close to where it curves around the occipital artery – via a miniscule filament, the ramus lingualis vagi. In addition to innervation via the pharyngeal plexus, the inferior constrictor, namely cricopharyngeus, also receives contributions from braches of the vagus nerve, the external and recurrent laryngeal nerves.

Sensory fibres predominantly originate from the glossopharyngeal nerve to provide the sensory supply to the majority of the oropharynx. The valleculae lying within the oropharynx are, however, supplied by the internal laryngeal nerve off the vagus nerve as well as by the lesser palatine nerve, a branch off the maxillary division of the trigeminal nerve. Part of the nasopharynx is supplied principally by the maxillary branch of the trigeminal via the pterygopalatine ganglion. Sensation within the laryngopharynx is via the internal laryngeal nerve.

The sensory supply of the palate originates from branches of the pterygopalatine ganglion, namely the greater and lesser palatine nerves, which travel with the arteries of the same name. The site of their entry into the palate is a useful landmark for performing local anaesthetic blocks, as it enters 1 cm medial to the region of the second molar.

LYMPHATIC DRAINAGE OF THE PHARYNX

The lymphatic drainage of the pharynx is complex due to the length of the structure and the rich lymphatic supply. It is especially important in malignant disease, as metastatic spread is particularly common from cancers affecting the pharynx. Awareness of this pattern of spread is important when assessing which parts of the lymphatics to treat prophylactically.

The nasopharynx lymph drains to the retropharyngeal lymph nodes and deep cervical lymph nodes. In nasopharyngeal cancer, the nodal stations involved are principally the retropharyngeal nodes and level 2 nodes (in approximately 70% of cases), with spread to levels 3, 4 and 5 also occurring to a lesser extent (45%, 11% and 27% respectively).

Lymphatics channels within the oropharynx pierce through the superior constrictor to principally drain into the deep cervical lymph nodes, particularly the jugulodigastric or tonsillar node situated just below the angle of the mandible (level 2). On occasion, lymph can also drain into level 3 and 4 nodes, although drainage to these distant levels without affecting the upper neck nodes is uncommon.

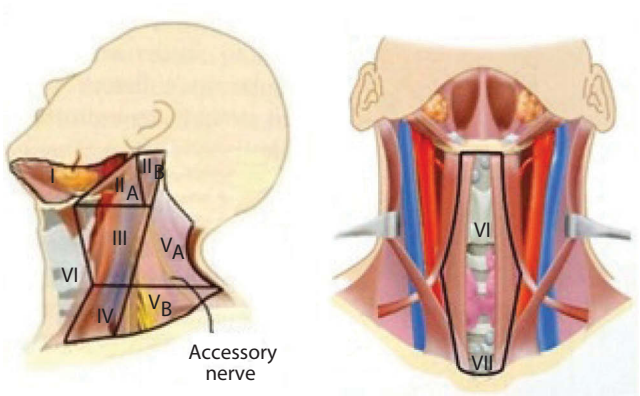


Figure 47.12 The lymph nodes of the neck.

The hypopharynx drains to all levels of the deep cervical nodes, principally to levels 2, 3 and 4. Overall the commonest level of drainage is to level 3 (**Figure 47.12**).

ANATOMY OF THE OESOPHAGUS

INTRODUCTION

The immediate continuation of the pharynx and a conduit for food and fluids into the stomach is the 25 cm long oesophagus, a flattened muscular tube that extends from the level of the inferior border of the cricoid cartilage (sixth cervical vertebra) to the cardiac orifice of the stomach at the level of the eleventh thoracic vertebra. It is the narrowest part of the digestive tract (excluding the appendix) and has three anatomical narrowings along its course. It courses anterior to the vertebral column in the neck and passes through the superior and inferior mediastinal spaces on the posterior aspect of the thorax to the diaphragm, which it penetrates via the oesophageal hiatus at the level of the tenth thoracic vertebra. Thus the oesophagus has a cervical, thoracic and abdominal component. Within the neck, despite originating in the midline, it gradually veers to the left until it reaches the root of the neck. From there it continues again in the midline, and is back to its original vertical orientation. At the level of the fifth thoracic vertebra, it veers yet again to the left but reverts back to being a midline structure. At the level of the seventh thoracic vertebra, it veers to the left again and continues in this course until it pierces through the oesophageal hiatus of the diaphragm. As it descends from the cervical region into the thoracic and then abdominal region, the oesophagus also follows the curvatures of the vertebral column in the anteroposterior plane.

Knowledge of the oesophagus is of considerable interest to otolaryngologists; rigid oesophagoscopy is a relatively common procedure, pharyngeal pouch repair may be complicated with perforations of the oesophagus, foreign bodies routinely lodge within the oesophagus, strictures of the tube require the skilled use of dilators to avoid complications. An intimate knowledge of the anatomical constrictions and oesophageal relations are vital to avoid formation of false passages and inadvertent entry either into the mediastinal cavity or the adjacent pleural spaces and lungs.

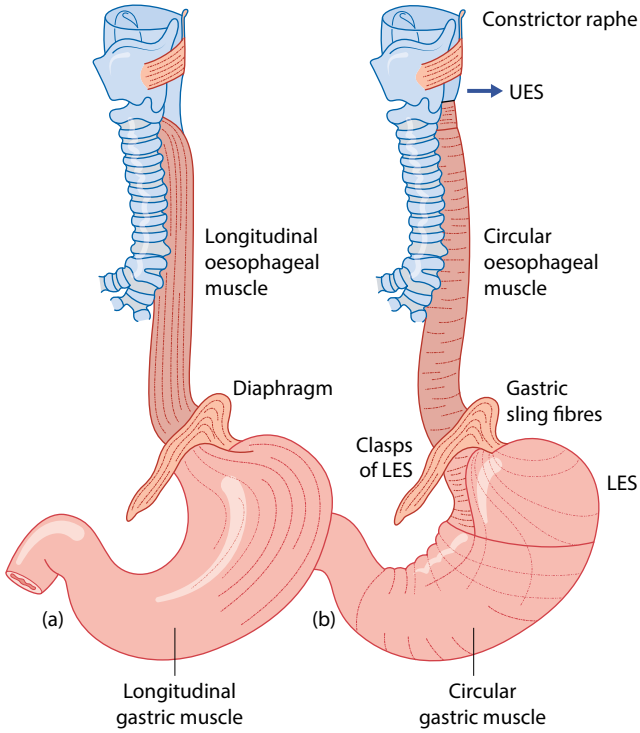


Figure 47.13 Longitudinal and circular muscle in the oesophagus.

Muscles of the oesophagus are shown in **Figure 47.13**.

SUBDIVISIONS OF THE OESOPHAGUS

The oesophagus has three arbitrary subdivisions, primarily based on its course from neck to abdomen as it traverses the neck, the thorax and enters into the abdomen (see above). These are the cervical, thoracic and abdominal oesophagus.

Cervical oesophagus

The superiormost region is the cervical oesophagus. It lies immediately posterior to the trachea and is adherent to the trachea via loose connective tissue. Bilaterally, close to a groove between the two structures, the recurrent laryngeal nerves pass superiorly to pass into the larynx behind the cricothyroid joint to innervate the intrinsic musculature of the larynx. At the level of the thyroid gland, the oesophagus is generally slightly to the left of midline. Posteriorly, the oesophagus rests on the vertebral column formed at this level by the bodies of the sixth and seventh cervical vertebrae and the prevertebral fascia overlying the longus colli muscle. It is flanked on both sides by the common carotid artery, within the carotid sheath, as well as the lower poles of the thyroid gland. To its left, the thoracic duct ascends for a short distance on its way to deposit its contents at the confluence between the subclavian vein and the internal jugular vein.

Thoracic oesophagus

Within the superior mediastinum, the thoracic oesophagus runs slightly to the left of midline initially before passing posterior and to the right of the aortic arch to enter the posterior part of the inferior mediastinum (**Figure 47.14**). Here, it descends to the right of the descending thoracic aorta, although it veers to the left along its course to the oesophageal hiatus of the diaphragm and thus is situated anterior to the descending aorta in the inferior part of the thorax.

In the superior mediastinum, the anterior relations of the oesophagus are the trachea and the left recurrent laryngeal nerve. Its left lateral relations at this point are the terminal part of the aortic arch, the left subclavian vein, the thoracic duct, the left recurrent laryngeal nerve and the left pleura. In the posterior mediastinum, the anterior relations are the left main bronchus, the tracheobronchial lymph nodes, the pericardium and the left atrium. Immediately posterior to the oesophagus are the vertebral bodies of thoracic vertebrae one to four, the thoracic duct sandwiched between the azygos vein and the descending aorta, as well as the right posterior intercostal arteries, and the hemiazygos and accessory azygos veins. At the terminal end of the thoracic part, the descending aorta lies between the oesophagus and the vertebrae.

The left side of the oesophagus lies close to the mediastinal pleura superior to the arch of the aorta except where the thoracic duct and left subclavian artery intervene. The right side of the oesophagus is adjacent to the mediastinal pleura and lung except where the azygos vein intervenes. The thoracic duct enters the thorax through the right side of the aortic hiatus of the diaphragm and runs up along the right side of the oesophagus until, at the level of the fifth thoracic vertebra, it crosses to the left side. From here, it continues up to drain into the junction of the internal jugular vein and the subclavian vein.

The left and right vagus nerves form a plexus that covers the oesophagus, giving off cardiac and pulmonary branches. Lower in the thoracic oesophagus, the plexus once again forms a number of nerve trunks that accompany the oesophagus through the oesophageal hiatus.

CONSTRICTIONS OF THE OESOPHAGUS

The thoracic oesophagus has three constrictions that are not evident in the collapsed oesophagus but can be visualized when air is insufflated into the oesophagus, as is done during oesophagoscopy or when contrast medium is swallowed for radiological examination. The narrowest part of the oesophagus is at the cricopharyngeal sphincter, the commencement of the oesophagus and point of termination of the pharynx. This is generally at approximately 15 cm from the incisor teeth. Below this point, three further anatomical constrictions can be expected along the course of the oesophagus through the thorax and into the abdomen (**Figure 47.15**).

The first constriction within the oesophagus itself is formed when it is crossed over by the arch of the aorta at approximately 22 cm from the incisor teeth. This is immediately followed by a further constriction occurring at approximately 27 cm from the upper incisor teeth and caused by the left main bronchus crossing over it. These two constrictions are often considered as one constriction. The final constriction, at 38 cm from the incisor teeth, occurs as it passes through the diaphragm just prior to the start of the abdominal part of

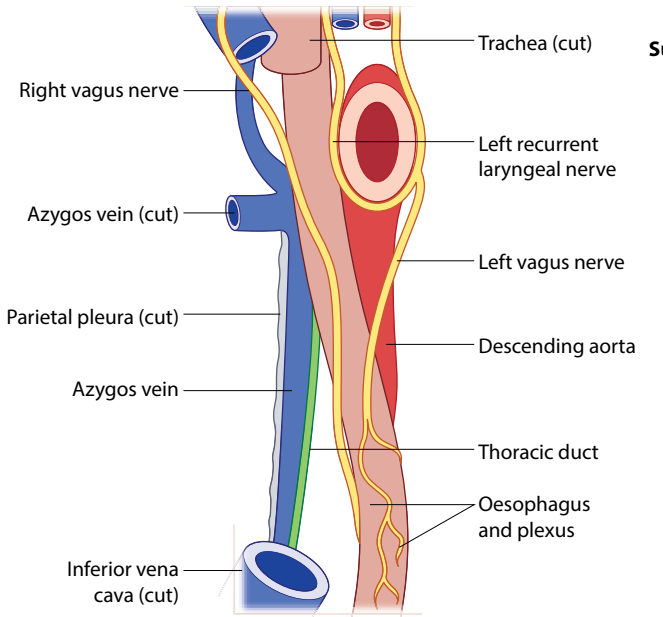


Figure 47.14 The intrathoracic part of the oesophagus.

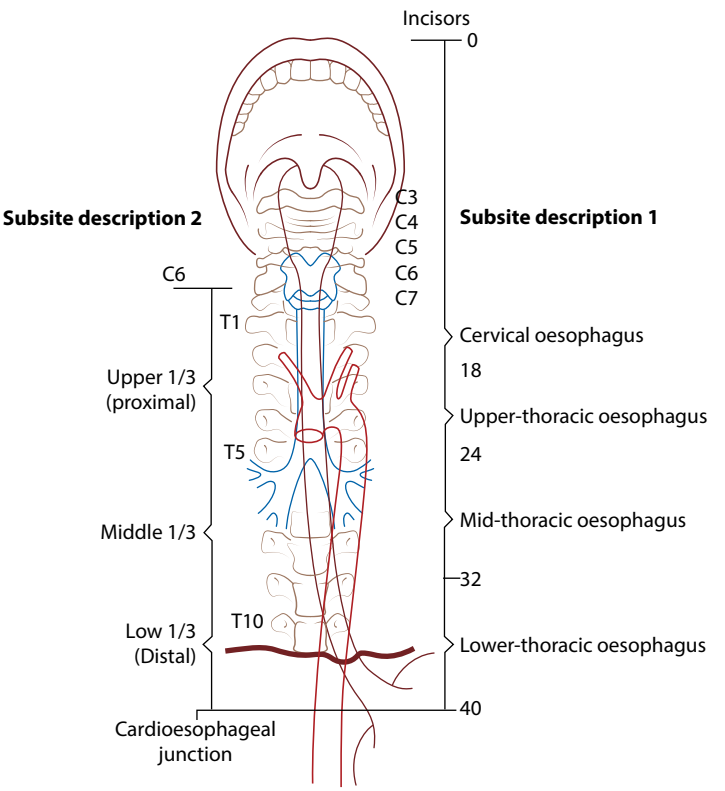


Figure 47.15 Oesophageal constrictions.

the oesophagus. Should the left atrium be enlarged for any reason, it can occasionally cause indentation onto the oesophagus on the anterior aspect just below the left main bronchus.

These constrictions and knowledge of the measurements from the incisor teeth are of considerable importance clinically when instruments are passed through the oesophagus, which can cause serious damage should the functional anatomy of this area not be fully appreciated. All measurements are approximate for an adult.

Abdominal oesophagus

The abdominal section of the oesophagus is the shortest of the three sections and emerges through the right crus of the diaphragm at the level of the tenth thoracic vertebra, left of the midline. It lies in the oesophageal groove on the posterior aspect of the left lobe of the liver before passing to the left to enter the stomach. The right border of the oesophagus continues into the lesser curvature of the stomach in the shape of a truncated cone to become continuous with the cardiac orifice of the stomach. It is covered with peritoneum overlying the lesser sac. The left border of the oesophagus, however, is separated from the fundus of the stomach by the cardiac notch. It is contained within the superior part of the lesser omentum due to the peritoneal coverings that encompass it on its lateral and anterior aspects. On its posterior surface, peritoneum is reflected to the diaphragm. This is part of the gastrosplenic ligament connecting the stomach and the spleen. The oesophageal branches of the gastric artery travel through this ligament to arrive at the abdominal part of the oesophagus. Even further posteriorly are the left phrenic artery and the left crus of the diaphragm. The vagus nerve travels alongside the oesophagus but its relation to the structure is varied as the oesophagus traverses the diaphragm. The left vagus nerve, with its two to three trunks, is usually located on the anterior aspect. The thick, single right vagus nerve is situated posterior to the oesophagus.

OESOPHAGEAL WALL

The oesophageal wall is made up of four discrete layers. These are, from the lumen outwards, the mucosa, submucosa, muscularis propria and adventitial layers. The oesophagus lacks a distinct serosal covering. As a result, direct tumour spread is easily facilitated, often complicating surgical resection. In addition, in the event of oesophageal perforation, the absence of a serosal layer makes repair more difficult.

Mucosal layer

The mucosal layer is lined by a continuation of the non-keratinizing stratified squamous epithelium which has an abrupt change in the lower oesophagus on entering into the stomach at the so-called Z line. This jagged line at the gastro-oesophageal junction is the area at which the mucosa changes to columnar epithelium which lines the stomach. The oesophageal mucosa above is characteristically greyish-pink and smooth; the gastric mucosa below is reddish-pink and has a number of bulges and depressions on its surface. This change is clearly visible at endoscopy. In life, the oesophageal mucosa is thick; superiorly it is more red and thicker. Inferiorly, it is paler. At rest, the mucosa is arranged into longitudinal folds; which disappear upon distension of the oesophagus.

The mucosal layer has three distinct sub-layers: (i) non-keratinizing epithelium which covers the entirety of the inner surface of the oesophagus, with the exception of the lower oesophageal sphincter, at which squamous and columnar epithelium meet and coexist; (ii) a thin layer of connective tissue, the lamina propria; and (iii) the muscularis mucosae comprising irregularly arranged longitudinal fibres of smooth muscle extending from the oesophagus into the rest of the gastrointestinal tract.

Submucosal layer

The submucosal layer loosely connects the mucosa to the underlying muscular layer. It also penetrates into the longitudinal ridges of the lumen of the oesophagus. It contains the larger blood vessels and Meissner's plexus of parasympathetic fibres and numerous mucinous glands, lymphocytes and plasma cells. The oesophageal mucinous glands are small tubulo-acinar glands. These mucous glands have acini arranged like grapes on a stem. Secretion from these glands is important in oesophageal clearance as well as to render the oesophageal tissue resistant to acid. The elastic fibres of the submucosal layer play an important role in closing the lumen after the dilatation caused by peristalsis.

Muscular layer (muscularis externa)

The muscular layer is responsible for oesophageal motor function and is composed of an outer longitudinal and an inner circular coat of muscle fibres. These layers are typical to the intestine. The longitudinal layer forms a continuous coverage of the oesophagus, apart from the upper 4 cm. Here, the fibres diverge posteriorly to form two longitudinal bands which pass in a superior and anterior direction to attach to the cricoid cartilage. The circular fibres are continuous, on the posterior aspect, with the corresponding muscular layer of the constrictor muscle superiorly and the muscles of the stomach. Generally, the longitudinal layer is the thicker of the two layers.

The proximal third of the oesophagus consists exclusively of striated (or skeletal) muscle, whereas the distal third is made up of smooth muscle. Between these two regions is a mixture of both striated and smooth muscle, a zone of transition in which the proportion of smooth muscle increases continuously, so that it, alone, exists in the lower part of the oesophagus. The oesophagus has two physiological sphincters, namely the upper oesophageal sphincter, which is composed principally of the lower

fibres of cricopharyngeus and is therefore anatomically strictly outside the oesophagus, and the lower oesophageal sphincter at the junction of the oesophagus and stomach. The physiological function of these is dealt with in Chapter 48, Physiology of swallowing.

Adventitial or fibrous layer

The external fibrous layer of the oesophagus consists of adventitia and dense connective tissue with elastin fibres and also contains small vessels, nerve fibres and lymphatic channels. This covers the oesophagus and connects it with its neighbouring structures. As mentioned above, the oesophagus is unique in that it has no serosal layer, unlike the rest of the digestive tract.

BLOOD SUPPLY OF THE OESOPHAGUS

The cervical oesophagus gets its main blood supply superiorly from the inferior thyroid artery of the thyrocervical trunk. The thoracic section of the oesophagus gains some of its blood supply segmentally from branches of the descending aorta or by branches of the bronchial and oesophageal arteries. Approximately five oesophageal arteries arise from the aorta anteriorly and these descend to supply the oesophagus by forming a vascular chain on the oesophagus itself. The vascular chain anastomoses with the branches of the inferior thyroid artery above as well as with the branches of the left phrenic and left gastric arteries below. The abdominal oesophagus is thus supplied by the left gastric and left inferior phrenic arteries. A dense blood supply and the anastomotic nature of the oesophageal blood supplying it render the organ virtually immune to infarction.

The venous drainage is initially via a complex network or plexus of veins that lies in the submucosal layer. Drainage from here is into a perioesophageal venous plexus, the point of origin of the oesophageal veins. The cervical oesophagus drains into the inferior thyroid vein via the brachiocephalic veins. The thoracic part of the oesophagus drains predominantly into the azygos veins, but also to a lesser extent into the hemiazygos and intercostal veins in the thorax, as well as to the bronchial veins. Inferiorly, the abdominal oesophagus drains into the left gastric vein. It meets the oesophageal vein at the lesser curvature of the stomach and drains from here into the portal vein. Knowledge of this anastomosis occurring at the level of the central diaphragmatic tendon (vertebral level T8) between the portal and systemic venous system is useful when diagnosing oesophageal varices. Portal obstruction can result in the formation of oesophageal varices in these veins, and throughout the upper gastrointestinal system, which, if ruptured, can result in life-threatening haemorrhaging.

INNERVATION OF THE OESOPHAGUS

The oesophagus also receives its innervation from dual sources. This is traditionally referred to as the sympathetic and parasympathetic supplies, although innervation is received from the vagus as well as the spinal nerves via different pathways and synapsing in different nuclei. Its sympathetic supplies, both motor and sensory, are from the spinal segments of T1–T10. Sympathetic and parasympathetic innervation regulates smooth muscle activity and glandular secretion.

The upper striated muscles of the oesophagus are supplied by multiple small branches arising from the recurrent laryngeal nerves as well as postganglionic sympathetic fibres from the middle cervical ganglia hitching a ride along the inferior thyroid arteries. The more distal smooth muscle fibres of the lower oesophagus are supplied by the oesophageal plexus, a meshwork of parasympathetic and sympathetic fibres hosted by the vagus and recurrent laryngeal nerves below the level of the lung roots.

Intrinsic innervation of the oesophagus is provided by the thin nerve fibres and numerous ganglia of the intramural myenteric and submucosal plexi. Auerbach's plexus (also known as the myenteric plexus) is formed by the ganglia that lie between the longitudinal and the circular layers of the tunica muscularis. Meissner's plexus (also known as the submucous plexus) is formed by those ganglia that lie in the submucosa. Despite their different functions – Auerbach's plexus regulates contraction of the outer muscle layers and Meissner's plexus regulates secretion and the peristaltic contractions of the muscularis mucosae – they are interconnected by a network of fibres.

The perception of pain in the oesophagus is limited and is more likely to be due to stretching of the external muscular coat rather than actual mucosal awareness. This may explain why localization of pain to a site within the oesophagus is very difficult, although referred pain is common.

LYMPHATIC DRAINAGE OF THE OESOPHAGUS

An extensive submucosal lymphatic system exists within the oesophagus. The upper oesophagus drains into the lower deep cervical and paratracheal and upper mediastinal nodes. The thoracic section drains into the posterior mediastinal nodes and the tracheobronchial nodes. The abdominal section drains into the left gastric nodes as well as the coeliac nodes. The lymph drainage, however, does not follow this pattern strictly. Within the walls of the oesophagus, there are lymphatic channels which allow the flow of lymph within the organ itself. Some lymph may pass directly into the thoracic duct.

KEY POINTS

- Within the nasopharynx, the **pharyngotympanic/auditory tube** connecting the middle ear to the pharynx opens out. This connection helps to equalize pressure behind the tympanic membrane within the ear but, as with all connections, it has the potential for spreading infections from one site to the other, predominantly from the nasopharynx to the middle ear.
- Although there is plexiform venous drainage around the tonsillar hemicapsule of the palatine tonsils, the paratonsillar vein (or external palatine vein) runs within the capsule and is the usual culprit for a **post-tonsillectomy bleed**.
- The glossopharyngeal nerve also supplies the middle ear (the tympanic branch) and thus **referred pain** to the ear during an episode of tonsillitis or after any surgical procedure in the peritonsillar area is not unusual.
- Nasopharyngeal tonsils can be problematic when inflamed in **adenoiditis**. The lymphoid tissue here is prominent in children but generally atrophies after puberty. Enlarged adenoids can cause mouth-breathing, and may block the pharyngotympanic tube.
- **Peritonsillar abscesses** – quinsies – occur outside the tonsillar hemicapsule. The internal carotid artery is about 2.5 cm lateral and posterior to the tonsil and this is thus a potential danger zone when incising peritonsillar abscesses.
- The valleculae, between the dorsum of the tongue and the epiglottis, is a common site for **small foreign bodies** to lodge.
- The piriform recesses at the side of the laryngeal inlet are also potential sites where **foreign bodies may lodge**. The space also allows for **malignancies** to grow to a substantial size asymptomatically, at which point they present with metastatic cervical lymphadenopathy.
- Killian's dehiscence, at the junction formed by the two muscles (thyropharyngeus m. and cricopharyngeus m.) forming the inferior constrictor, is a site of potential weakness. A defect or weakness here can result in the formation of a **pharyngeal diverticulum**.
- The cricopharyngeus muscle, which is circular and a sphincter, remains closed most of the time. This can pose problems when an **endoscope** is required to get beyond this point into the oesophagus but is generally overcome by getting the patient to swallow, and thus relax the sphincter momentarily.
- Three anatomical constrictions of the oesophagus, measured by their distance from the incisor teeth to allow for endoscopic examinations, are at 15 cm, 23–27 cm and 38 cm.

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CHAPTER
48

PHYSIOLOGY OF SWALLOWING

Joanne M. Patterson and Stephen McHanwell

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SEARCH STRATEGY

Data in this chapter are based on a PubMed search using the keywords: swallowing, transit times, pharyngeal pressure, bolus formation, mastication and taste.

INTRODUCTION

Swallowing requires the coordinated activity of muscles in three regions of the head and neck: the oral cavity, the pharynx and larynx, and the oesophagus. This complex sequence of motor behaviour is part reflex and partly under voluntary control. It has been extensively investigated using a variety of techniques including videofluoroscopy, endoscopy, radiography, ultrasound, electromyography (EMG) recording and functional MRI, together with observations on individuals with dysphagia. Swallowing as a motor behaviour is so complex that some details have remained difficult to resolve. The literature is often contradictory, particularly the earlier studies based on inferential analysis of radiographic data. Careful analysis of swallowing using newer techniques shows that there is a surprising amount of variation between individuals. This chapter will survey the current state of knowledge concerning the normal anatomy and physiology of swallowing and what might be considered as the limits of normality, essential to the understanding of dysphagia. Neural control and the coordination of breathing and swallowing will also be addressed.

STRUCTURES INVOLVED IN SWALLOWING

Swallowing involves the passage of a bolus of food or liquid from the oral cavity to the stomach via the pharynx and oesophagus. During this passage, the bolus passes over the entrance to the laryngeal vestibule which thus needs to be closed if food or liquid is not to enter the airways (**Figure 48.1**). The musculature involved is extensive, including muscles controlling the position of the lips, elevation and depression of the jaw, position and degree of contraction of the tongue, the degree of constriction and length of the pharynx, closure of the laryngeal inlet, the cricopharyngeal sphincter and the muscles of the oesophagus and oesophageal sphincter. This section will simply outline some key anatomical features and functions of the structures involved. For a more detailed account of the anatomy of the relevant muscles and the larynx, a suitable textbook of anatomy should be consulted.[1]

The elevators and depressors of the jaw play a key role in bolus preparation before the swallow is initiated by grinding and reducing the food between the teeth. Two groups of muscles that move the jaw can be recognized: the supramandibular muscles and the inframandibular muscles. The supramandibular muscles are attached between the mandible and the skull and comprise the muscles of mastication, temporalis, masseter and the medial and lateral pterygoid muscles. As the consequence of their attachments, they principally act as jaw elevators, though the inferior head of lateral pterygoid is active during jaw depression by acting to protract the mandible. The inframandibular muscles are composed of the suprahyoid and infrahyoid muscles of the neck and act indirectly on the mandible through their actions in raising or lowering the hyoid bone. Bolus formation is also a function of the

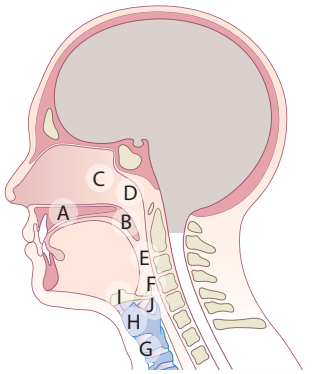

Figure 48.1 A mid-sagittal section of the head and neck showing the location of the major structures involved in swallowing. A, hard palate; B, soft palate; C, nasopharynx; D, pharyngeal isthmus; E, oropharynx; F, laryngopharynx; G, cricoid cartilage; H, thyroid cartilage; I, hyoid bone; J, laryngeal inlet.

muscles of the tongue. Two groups of tongue muscles can be recognized, the intrinsic muscles of which are mainly responsible for changing the shape of the tongue. The extrinsic muscles with one attachment outside the tongue are responsible for altering the position of the tongue in the mouth. The actions of these two groups of tongue muscles are not entirely independent since changes in tongue shape will result in changes in tongue position and vice versa. For example, flattening the tongue by the verticalis muscles will protrude the tongue as its bulk is displaced, while downward movement of the tongue by the hyoglossus muscle will tend to lower the sides of the tongue but not its centre. The actions of the tongue and jaw muscles in bolus formation are aided by that of the sphincter of the lips orbicularis oris in maintaining a seal, the buccinator muscle of the cheek in returning food from the vestibule into the oral cavity and thus ensuring that food remains in place between the occlusal surfaces of the molar teeth, and the soft palate in preventing nasal regurgitation and premature movement of material into the oropharynx. It is now recognized that the palate does not seal off the oropharynx completely during bolus formation (see below).

On leaving the oral cavity, food enters the pharynx, a midline tube approximately 15 cm long, continuous with the oesophagus inferiorly while above the soft palate it is continuous with the nasal cavities anteriorly. The anterior wall of the pharynx below the soft palate is incomplete and composed of the posterior part of the tongue superiorly and the larynx inferiorly, with the laryngeal inlet forming a posterior-facing opening on the anterior wall. As a consequence of these anterior anatomical relationships, the pharynx is divided into three regions: nasopharynx, oropharynx and laryngopharynx, corresponding to those structures that lie anterior to the appropriate part of the pharyngeal tube.

The pharyngeal wall proper is composed, like the whole of the gastrointestinal tract, of four layers or coats which, from the outside in, are the areolar, the muscular, the submucous and the innermost mucous membrane. The muscular layer is composed of circular and longitudinal muscles. There are three circular muscles – the superior, middle and inferior constrictors – with the inferior constrictor being further subdivided into a thyropharyngeus and a cricopharyngeus part. These constrictor muscles are arranged as a triad and are usually described as being arranged in the form of three stacked cups with the inferior constrictor being on the outside and the middle and superior constrictors lying inside. The fibres of the superior and middle constrictors extend inside the inferior constrictor to approximately the level of the vocal folds. With the exception of the cricopharyngeus, the constrictor muscles are paired and attach to a posterior midline raphe. The cricopharyngeus forms a distinct sphincter, the cricopharyngeal sphincter, at the point where the laryngopharynx joins the oesophagus and it contains a high proportion of elastic fibres to aid its sphincteric function. There are two discrete longitudinal muscles on each side, the palatopharyngeus and the stylopharyngeus, which, despite their names, both attach inferiorly to the posterior border of the thyroid cartilage.

The larynx is formed of a series of cartilages in the wall of the upper part of the trachea, the main cartilages being the thyroid, cricoid arytenoid and epiglottis. The thyroid, cricoid and arytenoid cartilages articulate at two synovial joints – the cricothyroid and cricoarytenoid joints – formed between the cartilages of the same name. Movements at these joints result in changes of position of the vocal folds to allow lengthening or shortening, opening or closing. The larynx is suspended from the hyoid bone by the thyrohyoid membrane and thyrohyoid muscle. When the suprahyoid and infrahyoid muscles move the hyoid bone, they also alter the height of the larynx. The epiglottis projects above the hyoid behind the posterior part of the tongue and is attached to the posterior aspect of the thyroid cartilage. The epiglottis is capable of movements to aid in the closure of the laryngeal inlet, although the mechanism by which movements are produced remains unclear (see below). Attached between the epiglottis anteriorly and the arytenoid cartilages posteriorly is the quadrangular membrane, the superior margin of which forms the boundary of the laryngeal inlet. Within this superior border are the aryepiglottic muscles that control the inlet, together with the small thyroepiglotticus muscle that may help to depress the epiglottis to prevent aspiration. Adduction or closure of the vocal cords by the intrinsic muscles of the larynx provides a further line of defence to the accidental ingestion of food or foreign objects.

The oesophagus is a muscular tube continuous with the pharynx. It has a short cervical course before it enters the thorax where it lies posteriorly in the midline and descends, piercing the diaphragm and entering the stomach.

THE SEQUENCE OF EVENTS IN THE NORMAL SWALLOW

In any land-living mammal that does not normally swallow its food whole, different stages of swallowing can be identified as having evolved in order to ensure that food is transported from the mouth to the stomach safely.[2]

Swallowing is a continuous process with overlapping events that may be artificially divided into three distinct phases: oral (preparatory and transit phase), pharyngeal and oesophageal. This evolutionary division is also convenient for descriptive purposes. **Figure 48.2** illustrates the key stages in the swallowing process as traditionally described.

Oral phase for liquids

ORAL PREPARATORY PHASE

In the oral preparatory phase, liquids are taken into the mouth and held either on the floor of the mouth or against the hard palate by the upward movement of the tongue. Throughout this first phase, the soft palate is kept lowered by the contraction of the palatoglossus and palatopharyngeus. The posterior tongue is simultaneously elevated, thus preventing uncontrolled spillage of the bolus into the pharynx. Liquids require minimal processing and are marginally diluted with saliva before swallowing. The airways remain open during this phase. Traditionally, the oral cavity was thought to be sealed posteriorly but this may not always be the case, as described in the following section.[3]

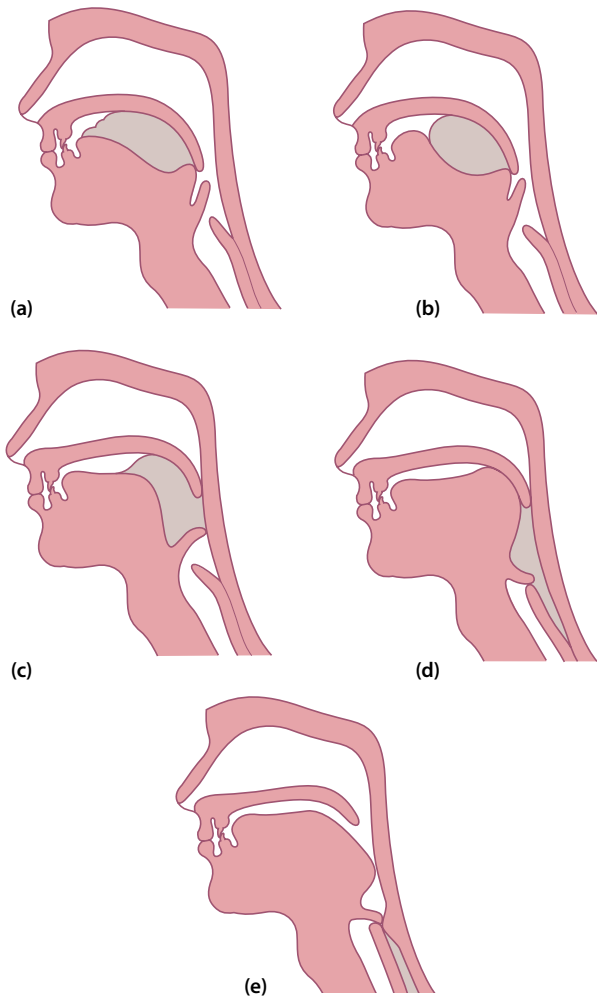

Figure 48.2 Oral and pharyngeal stages of a normal swallow: (a) oral phase, food is reduced and the bolus prepared; **(b)** the bolus is moved to the posterior part of the tongue; **(c)** the bolus contacts the trigger points in the oropharynx and the pharyngeal phase is initiated; **(d)** the bolus is moved past the closed larynx; **(e)** the bolus enters the oesophagus.

ORAL TRANSIT PHASE

The bolus is transported through the palatoglossal and palatopharyngeal arches into the oropharynx. The tongue is moved by the action of the intrinsic muscles together with the genioglossus elevating the tongue tip and blade of the tongue towards the hard palate. Orbicularis oris and buccinator remain contracted, keeping the lips and cheeks taut and the liquid central in the oral cavity. Liquid boluses are accommodated in a shallow midline gutter that forms along the dorsum of the tongue, probably as a result of the styloglossi and the genioglossi, aided by the superior longitudinal and transverse fibres of the intrinsic muscles.

A prerequisite for oral transit is mandibular elevation. Although the mouth does not have to be fully closed during swallowing, it is hard to swallow with the mouth more than a little open. The stabilization and elevation of the mandible is necessary for adequate lingual pressure generation. The proximity of the tongue to the palate helps to compress the bolus. The elevation and fixing of the mandible also assist the suprahyoid muscles in raising the hyoid bone. The elevation of the floor of the mouth is accompanied by lifting the tongue under the action of the stylohyoid. Simultaneously, the tongue is flattened, probably as a result of the contraction of the hyoglossus and some of the intrinsic lingual muscles, thus moving the bolus backwards. Patterns of lingual movement during swallowing can vary but, most commonly, the elevated, flattened tongue pushes the bolus against the hard palate, and the sides of the tongue seal against the maxillary alveolar processes, helping to move it posteriorly. The greatest amount of pressure appears to be generated by the anterior lingual segment.[4] Contraction of the styloglossus and mylohyoid completes the elevation of the back of the tongue. These tongue movements are simplified during sequential swallowing, as the frequency and speed of swallowing increase.[5] As the bolus reaches the back of the tongue, now deeply grooved, the soft palate is elevated by the levator and tensor veli palatini to protect the nasopharynx from the entry of food and to close the airways superiorly.

Oral phase for solids

When swallowing solid food, the process is slightly different. Food is mixed with saliva and reduced to smaller particles by the process of chewing. This can vary in duration considerably, from less than 1 second to as much as 10 seconds. When the bolus has been converted to a suitable consistency to be swallowed, it is transferred to the oropharynx, valleculae and posterior part of the tongue, where it may be retained for a few seconds prior to swallowing, sometimes referred to as ‘retrolingual loading’.[3]

During this time chewing can continue and the bolus is progressively added to, until a swallow is initiated and the pharyngeal phase begins. Thus, the oral preparatory, oral transport and pharyngeal phases overlap when solid food is being swallowed.

Chewing is essential to fragmenting solids, using a combination of shearing and compression forces. The mandible is moved by the action of the jaw elevators – the temporalis, masseter and medial pterygoid – and jaw depressors. Parotid salivary flow is increased in association with this action. The lips maintain a tight seal under the action of the orbicularis oris while the buccinator performs a similar function for the cheeks. In this way the sulci are closed, the vestibule normally remains empty, and any food that enters the vestibule is returned to the oral cavity proper. This, along with lateral and rotatory tongue movements, ensures that the food remains positioned under the occlusal surfaces of the molar teeth. Lateral and rotatory tongue movements ensure that the food is positioned under the occlusal surfaces of the teeth. Lingual forces will differ according to the physical properties of the bolus. These movements are cyclical in phase with movements of the jaw and hyoid bone. As the jaw is depressed, the tongue is also depressed and moves anteriorly. As the jaw is elevated, the tongue is retracted so that it no longer lies under the anterior teeth as they are brought together by jaw elevation. This helps to ensure that the tongue is not bitten during chewing.

It used to be thought that the soft palate was depressed throughout this phase, but it is now known that there is not a tight posterior seal and that the oral and oropharynx remain in communication.[6]

Pharyngeal phase

The pharyngeal phase begins at the point of the bolus leaving the oral cavity to enter the pharynx until it passes into the oesophagus. During this involuntary phase the respiratory and digestive streams cross and so it is important that this reflex behaviour occurs as automatically as possible to prevent blockage of the airways or aspiration into the lungs. As the bolus is moved back by the tongue to enter the pharynx, a sequence of events is initiated that ensures that the airways are protected during bolus transport. Diaphragmatic contraction is inhibited making simultaneous breathing and swallowing impossible under normal circumstances.[7] The nasopharynx is sealed off from the oropharynx by activation of the superior pharyngeal constrictor and contraction of a subset of palatopharyngeal fibres to form a variable, ridge-like structure (Passavant's ridge) against which the soft palate is elevated.

As the bolus enters the oropharynx and touches key trigger points, a patterned response is initiated in which the constrictors relax to dilate the pharynx, while the pharynx and larynx are raised by the longitudinal muscles. Solid boluses are propelled over the epiglottis by the action of the constrictors contracting in sequence. The larynx is then closed by contraction of the muscles of the laryngeal inlet, predominantly those of the aryepiglottic folds. The initiation of swallowing involves contact of the food with the palatoglossal and palatopharyngeal (faucial) arches or with the mucosa overlying the posterior pharynx in the region that is innervated by the glossopharyngeal nerve. Work conducted using simultaneous videofluoroscopy and endoscopy suggests that the 'trigger point' for this initiation may be the 'summation of afferent signals for the entire oropharyngeal sensory field', rather than a single point.[3] However, this may not be the case for the swallowing of secretions, as saliva may gather as deep as the piriform sinuses, until a critical mass is reached upon which a swallow response is triggered. Bolus properties may also influence this timing, for example, carbonated drinks or cold fluid temperature can reduce these latency times.[8] Bolus material is seen in the valleculae and even the piriform sinuses in 60% of liquid and 76% of solid swallows before the swallow is initiated.[3] This calls into question the term 'premature spillage' (where the bolus is viewed in the laryngopharynx prior to a swallow trigger) as an indicator of dysphagia. It is often said that, once the bolus of food has passed the palatoglossal and palatopharyngeal arches, swallowing becomes reflexive. While it is true that swallowing is automatic once initiated, many people can voluntarily delay their swallowing up to a certain point.

Lack of clarity exists around the precise temporal relationships of subsequent events involving movement of the food from the posterior part of the tongue into the oropharynx and airway protection. As the bolus is moved into the oropharynx, a reflex closure of the glottis is initiated in which there are preparatory movements of the vocal folds and the laryngeal inlet prior to a full closure of the larynx.[3] Endoscopic studies have shown that the first swallowing event is arytenoid movement towards the midline.[9, 10] These movements are even seen when the bolus enters the oral cavity.[10] More commonly, the true vocal folds achieve maximal closure prior to laryngeal elevation, but for some the glottis may not be fully adducted until elevation is complete.[10] Furthermore, it appears there may be variance from person to person and from swallow to swallow, with a range of laryngeal closure duration from 0.31 seconds to 1.07 seconds.[11] Events may alter according to bolus consistency and the nature of the swallow. For example, during sequential swallowing of drinks, some individuals retain an elevated laryngeal position; others demonstrate a pattern of laryngeal 'bobbing' with the larynx semi returning to a resting position between swallows. Apnoea onset occurs approximately 0.19 seconds prior to the elevation of the larynx.[7] A completely sealed larynx requires full adduction of the vocal folds and hence glottic closure by medial movement of the arytenoid cartilages. This is achieved by the combined efforts of the thyroarytenoid, interarytenoid and lateral cricoarytenoid muscles. The ventricular folds approximate, tensing of the edges of the laryngeal opening and lowering of the epiglottis.[7]

The bolus enters the pharyngeal space, which is widening as it is raised, said by some to resemble the engulfing of prey by a snake.[2] This is partly due to the relaxation of the pharyngeal constrictors and partly to the anterior

movement of the pharynx as the hyoid bone is drawn forward under the elevating action of the suprahyoid muscles. It is thought that the geniohyoid is largely responsible for displacing the hyoid anteriorly, and the mylohyoid superiorly.[12] Laryngeal elevation also occurs as the suprahyoid muscles move the hyoid bone anteriorly, contributing to pharyngeal dilation. Raising the larynx narrows the laryngeal inlet, moving it towards the pharyngeal surface of the epiglottis as the laryngeal cartilages move anteriorly, tucking under the bulge of the posterior tongue, i.e. out of the path of the bolus. This action helps to expand the hypopharyngeal space and relax the cricopharyngeal sphincter, which is also raised by several centimetres. The bolus moves into the oropharynx, contacting the epiglottis, which then moves downward. This movement is usually described as occurring in two distinct stages, with the first bringing the epiglottis from a vertical to a nearly horizontal position and the second moving the upper third of the epiglottis to below the horizontal to cover the narrowed laryngeal aditus. The precise contribution of active and passive mechanisms to this two-phase closure is unclear. Some authors state that both actions occur passively due to movements of adjacent structures and forces generated by compression of the pre-epiglottic adipose fat pad, and within the ligamentous attachments of the epiglottis, or by a combination of the two.[13, 14] Others claim that the second epiglottic movement is generated actively by the action of the thyroepiglottic and hyoepiglottic muscles.[15] In favour of an entirely passive mechanism, it has been claimed that these muscles are too sparse to generate adequate force and that some of their attachments are not consistent with such an action.[14] Throughout this stage of swallowing, respiration remains suspended.

As the food passes over the posterior part of the curved epiglottis, it is diverted into the lateral food channels and the piriform fossae. Evidence has shown that solids tend to go straight over the epiglottis, while liquids are diverted laterally. This is possibly a characteristic of bolus properties rather than swallow biomechanics.[3] Multiple swallowing post-bolus is often classed as a sign of impairment. Clearance swallows occur in the healthy population even with water, more so with older adults.[16]

The true and false folds guard the entrance to the airways with the true vocal folds adducted to prevent ingress of foreign bodies. The protective cough reflex can then be used to remove the object. This strong expiratory airflow is assisted by abdominal muscles and compression of the lungs.

The pharynx constricts behind the bolus as the superior constrictor muscle contracts. The bolus is carried down the pharynx by a coordinated peristaltic wave in which the three constrictor muscles contract in the appropriate sequence, driving the bolus towards the oesophagus. The head of the bolus moves faster than the wave of the pharyngeal contraction suggesting that the kinetic energy imparted to the bolus as it is expelled from the mouth may be sufficient to carry it through to the pharynx. The tongue driving force is a positive pressure that squeezes the bolus towards the laryngopharynx. It is generated by the upward movement of the tongue pressing the bolus against the contracting pharyngeal wall and requires a tight nasopharyngeal seal. A hypopharyngeal suction pump is caused by the elevation and anterior movement of the hyoid and larynx, which creates a negative pressure in the laryngopharynx, drawing the bolus towards the oesophagus, aided by a more negative pressure inside the oesophagus. The pharyngeal constrictors generate a positive pressure wave behind the bolus. Their sequential contraction may facilitate clearance of any pharyngeal wall or piriform sinus residue.

At the end of this phase, the bolus is propelled towards the cricopharyngeal sphincter. At rest, this sphincter is closed by active contraction. Prior to the bolus arriving and the sphincter opening, the cricopharyngeus relaxes. The sphincter is then opened actively by the combined action of the suprahyoid muscles in moving the larynx anteriorly and superiorly and passively by pressure from the arriving bolus.

Oesophageal phase

The oesophageal phase begins after the relaxation of the cricopharyngeal sphincter has allowed the bolus to enter the oesophagus. This is a true peristalsis in which a relaxation in front of the bolus and a constriction behind the bolus move it towards the stomach. Sequential waves of contractions of the oesophageal musculature subsequently propel the bolus down to the lower oesophageal sphincter, which opens momentarily to admit the bolus to the stomach.

Swallowing timings

The timings of the stages of swallowing have been extensively investigated. Once the food is of a suitable consistency to swallow, transit from the mouth to the oropharynx takes 1–2 seconds, with up to a further second for the bolus to traverse the pharynx to the cricopharyngeal sphincter. The bolus then passes through the oesophagus to the stomach. The time taken for oesophageal transit has been estimated by a variety of techniques. Healthy oesophageal clearance time for a single swallow is estimated at 10–15 seconds,[17, 18] although a shorter time of 3 seconds is needed for liquids.[2] In the preparatory stage, it is unclear what determines when the bolus is to be moved into the oropharynx. An important factor is likely to be bolus consistency as sensed by mechanoreceptors in the oral cavity. The sensory control of swallowing will be discussed below under ‘Neural control’.

NEURAL CONTROL

Neural control of the complex activity of healthy swallowing involves a number of different regions of the central nervous system (CNS). In common with all complex motor behaviours, swallowing is organized and coordinated by a hierarchical series of structures within the brain.

This extends from the motor neurons within the motor nuclei of the brainstem and spinal cord (for ventilation) up to the cortex. The act of swallowing, as with all movement, is regulated by sensory feedback, although the importance of this has only been fully recognized relatively recently.[19] There are probably still some areas of the CNS involved in swallowing that remain to be identified but there is a consensus as to the main regions involved. The initiation of swallowing is normally characterized as being either a voluntary act (volitional swallowing) or a reflex (reflexive swallowing) as the result of stimulation of the appropriate mucosa in the oral cavity. This might occur during saliva accumulation or by the presence of food or liquid. However, it is now recognized that this distinction is not absolute. During mastication, for example, a volitional act, the encountering of a hard object will cause mastication to cease, suggesting a continuum of control between the purely volitional and purely reflex components of swallowing.[20] Although there may be a continuum because of the fact that, as swallowing is partly a reflex activity and partly voluntary, its neural control is divided between two major regions of the brain: the cerebral cortex and the brainstem. Studies have shown that several regions of the cortex contribute to the voluntary control of swallowing. It is also recognized that, as with any voluntary movement, the movements of swallowing are also regulated by the basal ganglia and the cerebellum.[21, 22] Due to the close anatomical and physiological relationships between swallowing, ventilation and mastication, there is also extensive overlap in the brainstem areas controlling these functions. There is an absolute requirement that neural control of these various processes ensures that they are coordinated.

The cortical control of swallowing involves projections to numerous groups of motor neurons. The areas of the cortex that have been most frequently cited as being involved in the control of swallowing include the primary motor and sensory cortices, premotor and supplementary cortices, posterior parietal cortex, cingulate cortex (especially the anterior cingulate gyrus) and the insula and frontal operculum.[23] Corticobulbar projections to motor nuclei controlling muscle groups are bilateral but, in the case of projections controlling pharyngeal muscles, asymmetric so that one can speak of a swallowing dominant hemisphere. As is the case for speech, this asymmetry is not related to handedness but it is the left hemisphere that is usually stated as being swallowing dominant though not with the same high frequency as speech.[24, 25]

Within the cortex, evidence suggests that the frontal swallowing centre is organized somatotopically with different regions controlling different stages of swallowing. This is substantiated by studies employing transcranial magnetic stimulation of the frontal swallowing centre.[24] These studies show that the lower precentral gyrus and posterior inferior frontal gyrus control the oral phase of swallowing. The voluntary initiation of swallowing (oral phases, see above) involves bilateral areas of the prefrontal, frontal and parietal cortices. These include the face areas of both the primary sensory and motor cortex, as well as the prefrontal swallowing areas which are located just anterior to the face region of the precentral gyrus in the primary motor cortex, corresponding to Brodman's area. Stimulation here produces swallowing activity in the appropriate muscles of the oral cavity, pharynx, palate and larynx.[26] Volitional swallowing also activates the cingulate cortex, anterior cingulate gyrus, supplementary motor cortex and insula just prior to the onset of the swallow. It has been proposed that activity in these regions prior to the swallow occurring controls the initiation, including motivation to swallow, and planning of the act of swallowing.[23]

Reflexive swallowing (see 'Pharyngeal phase' above) is thought to involve primary motor cortex, premotor cortex and areas of sensorimotor cortex within the parietal lobe.[27, 28] In most people, swallowing control is asymmetrical with the projection from one hemisphere being larger than the other. It has been hypothesized that this explains both the prevalence of swallowing problems following stroke and the recovery that occurs in most patients over a period of weeks. Damage to the hemisphere that is the source of the greater projection to the swallowing structures in the brainstem would account for the initial difficulty. Recovery then occurs as the intact projection from the undamaged hemisphere is reorganized.[29]

It can be seen that both volitional and reflexive swallowing involve the primary sensory and primary motor cortices consistent with the role, more generally, of these cortical areas in the control of fine distal motor movement. As might be expected, sensory feedback is needed to control swallowing, just as would be the case for any other movement.[19] The satisfactory execution of swallow needs to take account of the properties of the bolus being swallowed such as its size, texture and consistency. These properties are relayed to the primary sensory and motor cortices during the reflexive phase where they influence the intensity and speed of pharyngeal muscle contraction to ensure that the bolus is safely moved through the pharynx and on to the oesophagus.[30, 31] This role of the motor and sensory cortex in controlling force of contraction of muscles is consistent with what has been observed in other volitional movements.

The inference from animal studies is that the control of swallowing is bilateral, but in humans the organization of corticobulbar projections from the cortex to the relevant motor nuclei appears more complex. Cortical projections to the muscles of the larynx, pharynx, palate and upper face are bilateral while projections to other muscles can be either unilateral or bilateral.[32]

Other cortical areas that have been implicated in swallowing include the frontal operculum, the orbitofrontal cortex and the superior temporal gyrus.[24] The insula lies deep to the lateral fissure and is covered by the operculae of the frontal, parietal and temporal lobes and strokes here can induce dysphagia.[33] In addition to its role in swallowing as outlined above, taste is also represented in this region. It has been suggested that the insula may be involved in integrating the taste of a swallow with the movement of swallowing. The superior temporal gyrus has also been identified as a possible region of the cortex involved in integrating taste, but also food imagery, with swallowing.[34] This suggests that cortical control of swallowing

is hierarchical, with precentral areas of the cortex being influenced by deeper and more caudal centres.[24]

Cortical control of movement is regulated by reciprocal projections between the cortex and basal ganglia and between the cortex and the cerebellum. It is becoming evident that these regions of the brain also play a part in the control of swallowing. The evidence that this is the case in humans comes mainly from investigations of swallowing disorders in disease. Connections pass from cortical regions through the basal ganglia and back to the cortex via nuclei in the thalamus in the form of a series of recurrent loops. The basal ganglia were first recognized as having a role in movement because of the very obvious movement disorders that occur in basal ganglia disorders such as Parkinson's disease. However, it is now recognized that the basal ganglia regulate many other aspects of cortical function. Disorders of the basal ganglia affecting movement can be characterized as hypokinetic, with too little movement (e.g. in Parkinson's disease), or hyperkinetic, with too much movement (such as in Huntington's chorea). The effects of Parkinson's disease upon swallowing are consistent with its effects upon movement generally, with hypokinetic tongue movements that impair transport of food into the pharynx, poor bolus formation and poor pharyngeal transport including slower laryngeal movements.[21] The cerebellum also has reciprocal connections with the cerebral cortical regions controlling movement and functions to monitor executions of movements and act as an error detector. Though there are relatively few investigations into the occurrence of dysphagia in cerebellar disease and the results are inconclusive, it would appear that the cerebellum does play a part in motor control of swallowing.[22]

The cortex is crucial in the voluntary initiation of swallowing and integration with movements of the face and associated structures. However, cortical structures are not essential for a coordinated swallow, which can occur in the presence of significant brain damage in these regions. There are important areas within the brainstem necessary for the control of swallowing and these are located particularly within the medulla. Descending pathways project to these medullary swallowing centres from the frontal swallowing areas within the cortex. These probably include pathways in both the dorsolateral and ventromedial descending systems through the ventral and lateral corticobulbar tracts. Whether swallows are volitional or reflexive, the pattern of the swallow is similar because it is the brainstem that executes the patterns of swallowing movements in both cases.

Most of our knowledge of the role of these regions in swallowing control comes from experimental studies in animals. The results of these studies clearly have limitations when one attempts to apply them to humans.[35] Within the medulla there are a number of neuron groups involved in the control of swallowing.[36] Swallowing is initiated by touch sensation or pressure from the liquid or food within the posterior part of the oral cavity, epiglottis or oropharynx. Thus, the nuclei receiving afferent input from these regions, which include the nucleus tractus solitarius and the spinal trigeminal nucleus, are very important. Afferent input from the jaw, muscles of mastication, lips and tongue is also essential to the control of swallowing, not just during the pharyngeal phase as outlined above but also during the oral phase. The oral cavity contains an unusually high concentration of mechanoreceptors. These protect delicate tissues from the high forces generated during mastication, to trigger the reflex and to sense the size and consistency of the bolus, also as part of the trigger mechanism.

The efferent pathways from the medulla and pons to the muscles involved in swallowing involve several cranial motor nuclei. The most important are the nucleus ambiguus for the muscles of the palate, pharynx and larynx, the hypoglossal nucleus for the muscles of the tongue, and the motor nuclei of the trigeminal and facial nerves for the muscles of the jaws and lips. In addition, motor neurons within the cervical spinal cord control the muscles of the neck including the infrahyoid muscles.

Between these input and output pathways are interposed two main groups of neurons that appear to be essential for the coordination and regulation of swallowing by the medulla. The first lies in the dorsal region of the medulla above the nucleus of the solitary tract. A second group lies more ventrally around the nucleus ambiguus. These two neuronal groups are sometimes referred to as the lateral and medial medullary swallowing centres. A variety of evidence, much of it emanating from the laboratory of Jean,[37] supports the view that these two neuronal groups are vital in the control of swallowing. The dorsal group would appear to be the site of convergence of sensory input from the various nuclei and is probably important in the sequencing of swallowing. The ventral group distributes outputs to the various cranial nerve motor nuclei. Outputs from this region are not simply excitatory. In any reflex system, excitation of agonist muscles and their synergists will be accompanied by inhibitory outputs to the corresponding antagonist muscles.

The correct sequencing of events for healthy swallowing is thought to be controlled by a central pattern generator (CPG).[37] CPGs are groups of neurons capable of generating outputs that will ensure the basic sequencing of a movement in time and space in terms of the muscle contractions needed for automatic movements such as swallowing, ventilation and locomotion.[38] The action of many CPGs is based upon pacemaker-type activity of a subset of neurons that is responsible for the initiation of the rhythmic activity.[38] In this respect, swallowing is similar to ventilation, and both of these motor behaviours are linked to masticatory movements.[39] Given the close relationship between swallowing and ventilation, it seems to be inevitable that there will be central coordination of these processes. The idea of a central mechanism coordinating and regulating respiration and swallowing was first hypothesized over 30 years ago.[40] The exact neural organization is still unclear[41] and is one of the many areas for further investigation for a fuller understanding of the control of swallowing.

RESPIRATION AND SWALLOWING

The act of swallowing involves a crossing of the stream of liquid and food with that of breathing and this occurs within

the pharynx. This crossing of the alimentary and ventilatory streams is an evolutionary consequence of the transition in vertebrates from sea to land living. A variety of mechanisms have evolved to ensure that, during normal swallowing or vomiting, no material can be aspirated into the lungs through the larynx. Aspiration can have serious consequences, such as asphyxiation caused by airway blockage, or occult aspiration with resultant complications, although recent work has shown that aspiration can occur, although rarely, in the absence of a swallowing problem.[42, 43]

Respiration and swallowing are inextricably linked, finely coordinated and are under tight neural regulation (see above). Efficient transport of food and drink to the oesophagus has to co-occur with maintenance of a safe airway and prevention of material entering the lower respiratory tract (**Figure 48.3**). The main sphincteric mechanisms protecting the airways are the soft palate, guarding the pharyngeal isthmus, and those guarding the laryngeal aditus. There appears to be an individual swallowing respiration pattern that matures in the teenage years and is remarkably consistent thereafter.[45] Even following laryngectomy, where there is no risk of aspiration, breathing continues to be suspended during a swallow.[46] Furthermore, the length of breathing suspension appears to be longer in this case group, which is thought to be associated with longer pharyngeal transit times, compared to individuals with a larynx.[47]

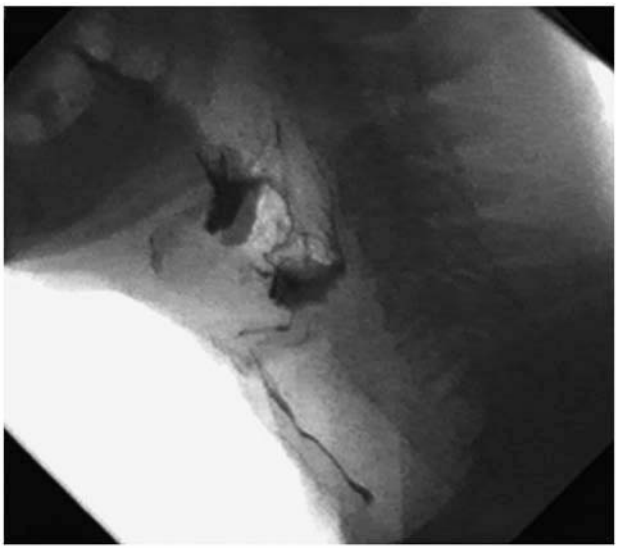

Figure 48.3 Aspiration into the upper trachea. Reproduced by permission of the BMJ Publishing Group from Leslie et al.[44]

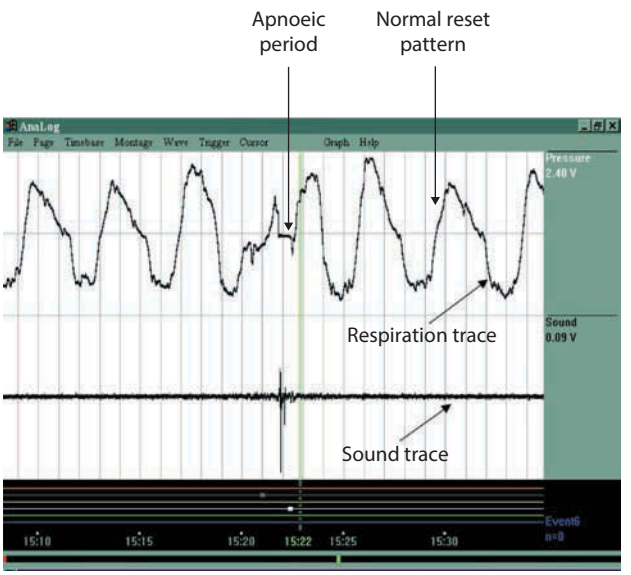

Figure 48.4 Swallow apnoea.

Swallow apnoea

Despite these methodological caveats, some general principles emerge. Clearly, ventilation has to be suspended during pharyngeal transit of the bolus (**Figure 48.4**). This is known as the period of swallow apnoea and is typically less than 1 second in length, corresponding to the duration of the reflex part of the swallow in its pharyngeal phase.[48, 49] The duration of apnoea increases with larger bolus volumes.[45] The effect of bolus consistency is less clear. There is evidence to suggest that solids increase apnoeas with the onset preceding the actual swallow, due to the risk posed by retrolingual loading,[50] but sample numbers are too small to be unequivocal.[49] Gender effects are conflicting, with men having longer durations due to differences in structure[51] and women having longer durations linked to increased cricopharyngeal opening.[45]

Phase of respiration when swallowing occurs

Swallowing tends to occur during the expiration phase of respiration. Expiration on swallowing is longer in duration, compared with quiet respiration.[52, 53] Expiration occurs after 80–100% of healthy swallows.[51, 54, 55] This is likely to be a protective mechanism, as any material left in the laryngeal vestibule post-swallow will be moved to the pharynx rather than sucked into the lungs. The diaphragm is responsible for a downward pull on the trachea and therefore the larynx. On the expiratory phase, at mid to low lung volume, this pull reduces, decreasing resistance and enabling the larynx to elevate during swallowing.[56]

Post-swallow inspiration is more common in populations with impaired swallowing.[55, 57] Furthermore, respiratory disorders such as chronic obstructive pulmonary disease (COPD) can compromise this phase regulation necessary for safe swallowing.[58] Much of the research on the respiratory–swallowing pattern is based on small single boluses of less than 10 mL. This pattern appears to alter with larger boluses, with a greater number of swallows occurring during the inspiratory phase[59] and require a greater lung volume than smaller boluses.[60]

TASTE

Taste buds are the receptors for taste and are located on the surface of the tongue, soft palate and epiglottis.

Each taste bud contains approximately 50–100 cells and has a life span of 10–14 days, and they are under constant regeneration.[61] They mature into one of three types of taste cell: type I detects salt; type II sweet, bitter and umami; and type III sour.[62] Saliva facilitates the movement of taste molecules to the taste bud and its composition is important for taste perception. Taste-related impulses are transmitted via the facial, glossopharyngeal and vagus nerves to the olfactory area of the cortex. The biomechanical swallowing response can alter with different taste flavours. For example, a sour bolus (e.g. lemon juice) may increase oral tongue pressures and tongue-to-palate contact times, although some dispute this.[63, 64] Furthermore, a sour bolus seems to have a longer transit and clearance duration in the distal oesophagus.[65, 66]

AGE EFFECTS

Infancy

In infancy, the anatomical relationships of the tongue, mandible and hyoid bone are much closer, requiring a highly coordinated pattern of suckle–swallow and respiration. Newborn feeding is primarily reflexive, and is dependent on a rooting reflex to latch on to a nipple or teat. Suckling requires the generation of intraoral pressure via lip seal around the source and the posterior tongue moving towards the soft palate. On average, infants generate two to seven tongue pumps per swallow.[67] Jaw movement creates an external pressure on the nipple or teat, encouraging liquid flow into the oral cavity. Swallow apnoea is mainly attributed to the larynx tucking under the tongue base and the arytenoids tilting forwards. Complete epiglottic inversion is not consistently present up until the age of 5 years.[68] From 0–5 months biting is an immature upwards mandible movement. The oral preparatory phase becomes more refined with the maturation of the oral cavity. Preliminary chewing begins with introduction of a more textured diet around 4–6 months. At approximately 1 year, the infant is more able to use grinding chewing movements, which continues to mature up to the age of 16.

Presbyphagia

Presbyphagia is defined as normal age-related changes in swallowing in healthy adults. Sarcopenia is the term used to describe the age-related decrease in muscle mass, strength and coordination. As a consequence of this process, older people have generally weaker oral phase movements, including reduced tongue strength.[69] Although still able to achieve adequate lingual pressures for swallowing, these pressures are generated more slowly than in younger people.[70, 71] Loss of dentition is common, reducing the number of opposing dental units for biting and grinding. Ill-fitting dentures may further hamper the oral preparatory phase. Changes to smell and taste also occur as part of the ageing process, impacting on the pleasure of eating and appetite. The pharyngeal phase is often longer in duration, with prolonged hyolaryngeal excursion. The pharyngeal wall can thin over time, creating a larger vault at rest, consequently reducing maximal constriction and pharyngeal pressure generation.[72–76] Sensory changes may account for a slower swallowing response time.[70]

Breathing and swallowing coordination may also decrease with age, with overall longer periods of apnoea. The combination of these changes may account for the higher incidence of laryngeal penetration of fluids in older individuals.[77, 78] Cricopharyngeal sphincter opening times are longer in duration. There is also a higher incidence of cricopharyngeal bars, which can impede bolus flow.[79] Overall, swallowing transit times are longer, but mean differences between younger and older age groups are small.[75, 76]

WHAT CONSTITUTES THE NORMAL SWALLOW?

Much of the data on the swallowing process comes from observations of populations with impaired systems. Studies of healthy groups are often of small numbers with young age ranges and many of the difficulties in swallowing are linked to age or age-related diseases. As more information emerges, the performance envelope of what constitutes 'normal' is growing. The process of swallowing a series of controlled volume and/or consistency boluses ('command swallows') does not equate with that of eating a meal.[6] When evaluating reports, the reader needs to be clear about age, sex, bolus type and other variables. It is clear that there is uncertainty and some scope for variation in the normal swallow.

KEY POINTS

- Swallowing is a cyclical and irregular process, not a stepwise progression.
- Healthy swallowing has a wide range of parameters.
- Neural control is divided between the cortex and the brainstem.
- Cortical control of swallowing is bilateral, although one hemisphere is usually dominant.
- Airway protection is activated in advance of the pharyngeal stage of swallowing.
- Impaired respiration patterns will affect swallowing and vice versa.

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CHAPTER 49

CAUSES AND ASSESSMENT OF DYSPHAGIA AND ASPIRATION

Helen Cocks and Jemy Jose

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SEARCH STRATEGY

Data in this chapter may be updated by a Medline search using the keywords: dysphagia, aspiration and swallowing, with focus on aetiology and diagnosis.

INTRODUCTION

Dysphagia

Dysphagia is a term used to describe difficulty with swallowing solids, liquids or both. It implies impairment of one or more of the phases of swallowing. Dysphagia usually arises as a complication of another health condition. It can be divided into oropharyngeal (high) dysphagia and oesophageal (low) dysphagia.

Dysphagia is common, with epidemiologic studies suggesting that as many as 22% of the population over the age of 50 are affected.[1, 2]

Aspiration

Aspiration is the entry of food or liquid into the airway below the true vocal folds.[3] It may be due to incompetent or inadequate airway protection, ill-timed, uncoordinated events before, during or after the swallow has triggered.[4] Silent aspiration is defined as foreign material entering the trachea or lungs without an outward sign of coughing or attempts at expulsion.

The link between aspiration and aspiration pneumonia remains elusive. Although an association has been identified in stroke patients there are no such data available in head and neck cancer (HNC) patients. In general, aspiration should be kept to a minimum but no clear guidelines exist as to the amount of aspiration that can be tolerated by patients with dysphagia. In a study looking at a mixed group of neurological and HNC patients, only 25% had a history of pneumonia despite over 50% presenting with aspiration.[4] Additional factors may need to be present for pneumonia to develop, such as poor oral hygiene, immobility,[5] neutropenia[6] and malnutrition.

Aspiration pneumonia has been shown to be the most common cause of mortality during hospital admission,[7] followed by nosocomial infections.[8] Prolonged, repeated aspiration of small amounts of material and chronic chest infections has been associated with the development of interstitial pulmonary fibrosis.[9] Diffuse alveolar scarring can occur across a period of time, reducing the ability of lung tissue to transfer oxygen to the bloodstream.

CAUSES OF DYSPHAGIA AND ASPIRATION

Dysphagia can be associated with anatomical, neurological, muscular or psychological causes, with aspiration often developing secondary to dysphagia. This section does not provide exhaustive coverage of possible causes but considers those causes more commonly seen in practice.

Congenital

Most patients present in the paediatric age group, though some may present later in life.

CLEFT LIP AND PALATE

Cleft lip and palate is often associated with nasal regurgitation. The child is unable to suck due to an inadequate seal within the oral cavity resulting from

the lip/palatal defect. This condition is usually picked up intrauterine or at routine neonatal examination soon after birth; however, mild variants of the condition can have a delayed diagnosis.

CEREBRAL PALSY

Cerebral palsy can cause significant oral muscular incoordination resulting in dysphagia, drooling and aspiration as saliva and food pools in the anterior floor of mouth and fails to trigger the pharyngeal phase of swallowing. Assessment involves clinical evaluation of swallow with videofluoroscopy (VF) in cases where there is concern about aspiration. Treatment options include speech therapy or physiotherapy measures, improving posture and relocation of submandibular ducts. Enteral feeding may be required in some patients.

VASCULAR RINGS

Vascular rings around the oesophagus due to malformation of great vessels, usually due to aberrant subclavian artery, double aortic arch or anomalous left pulmonary artery, can cause dysphagia. Extrinsic compression is noted on barium swallow and computed tomography (CT) angiography or magnetic resonance angiography (MRA) is diagnostic.

ATRESIS, CLEFTS AND FISTULA

Laryngeal clefts, tracheoesophageal fistula and oesophageal atresia all present with both dysphagia and airway difficulties depending on the type and severity of the condition. Diagnosis is made at endoscopy.

CONGENITAL VOCAL CORD PALSY

Congenital unilateral vocal cord palsy usually presents with a hoarse cry. There can be swallowing difficulties and aspiration during feeding. Diagnosis is made on endoscopy.

Infective

Infections of the oral cavity, larynx, pharynx and neck spaces can present with dysphagia. These are covered elsewhere in the book (see Chapter 69, Acute infections of the larynx; Chapter 51, Pharyngitis; and Chapter 40, Neck space infections)

Inflammatory

GASTRO-OESOPHAGEAL AND LARYNGOPHARYNGEAL REFLUX

The most common inflammatory process that causes dysphagia occurs secondary to gastro-oesophageal reflux disease (GORD).

GORD can result in erosions, ulcerations and even stricture formation in the lower oesophagus, which cause dysphagia and even food bolus impaction.

Dysphagia and other throat symptoms are also seen with laryngopharyngeal reflux (LPR), which can present with subtle laryngeal findings of erythema and oedema of posterior larynx; however, a recent systematic review has shown poor sensitivity and specificity for these findings, with many being seen in 64–93% of healthy subjects'[10] laryngoscopy findings. Flexible oesophagoscopy, 24-hour pH monitoring and oesophageal manometry studies often aid in making the diagnoses. GORD is discussed in greater detail in Chapter 53, Oesophageal diseases, and LPR in Chapter 77, Reflux disease.

PATTERSON–BROWN–KELLY SYNDROME

Patterson–Brown–Kelly syndrome is the association of dysphagia with atrophic gastritis and iron-deficiency anaemia. It affects mainly middle-aged and elderly women. The dysphagia is due to hyperkeratinization with web formation in the postcricoid region and can be seen on barium swallow, but it may not always be found at rigid endoscopy. The dysphagia and the hyperkeratinization are treated with iron replacement, but the web may need dilatation. The condition is associated with the development of postcricoid carcinoma in a small percentage of patients. Other features of iron deficiency anaemia – smooth tongue, angular stomatitis and koilonychias – may be seen.

EOSINOPHILIC OESOPHAGITIS

Eosinophilic oesophagitis (EoO) is an emerging condition characterized by oesophageal symptoms and infiltration of the oesophageal epithelium with eosinophils for which no other cause can be found. Other causes of eosinophilia need excluding and these include GORD, infection, malignancy, collagen vascular disease and inflammatory bowel disease (IBD). The condition has yet to be fully understood but it is thought that food allergy plays a large role in its development.

It was originally thought to be a form of GORD and a paediatric condition, but it is now known to be most common in middle-aged men. It is most frequently seen in Caucasians and has predominance in developed countries. Prevalence of EoO has increased in the last decade but this may be due to better understanding and detection. A community study in Sweden reported a prevalence of 4 in 1000 in 2016.[11] The British Society of Gastroenterology has set up a national registry.

Presenting symptoms of EoO can vary according to the age of the patient. In children, presentation is with failure to thrive and food refusal. Adolescents can have other symptoms such as chest/epigastric pain and vomiting and in adults symptoms can be of dysphagia, odynophagia and heartburn. Often adults present with food bolus obstruction.

Investigation is with gastroscopy and biopsy, and diagnosis is made on the finding of more than 15 eosinophils per high-powered field at microscopy. Allergy testing with RAST can be helpful in identifying allergens.

Management of EoO involves modification of diet. In severe situations, this involves exclusion of six predominate

food groups (wheat, dairy, fish, eggs, soy and peanuts) and the introduction of an elemental diet to allow improvement. Once improvement is seen at biopsy, food groups can be gradually reintroduced and the effect again judged by mucosal response at biopsy.

Other treatment is with topical steroids, a fluticasone or budesonide inhaler sprayed into mouth and swallowed dry with avoidance of eating and drinking for 30 minutes. A side effect of this is candidiasis.

Gold-standard monitoring of the condition is serial gastroscopies. Absolute blood eosinophil count has been found to correlate significantly with oesophageal eosinophil density and there is some evidence for use of absolute blood eosinophil level as a marker of disease.[12]

Stricture formation can occur as a complication of the condition and dilatation may be required.

SYSTEMIC AUTOIMMUNE DISORDERS

Systemic autoimmune disorders[13] are associated with dysphagia in a large proportion of cases, though the mechanism differs between disease groups. Diagnosis of this group of conditions is based on the clinical picture and autoantibody profile. Control of the disease with steroids and immunosuppressive drugs does not usually improve the dysphagia.

Scleroderma and 'CREST' syndrome

Scleroderma and 'CREST' syndrome (calcinosis, Raynaud's, oesophageal involvement, sclerodactyly, telangiectasis) are progressive disorders of connective tissue. Smooth muscle cells are replaced by collagen fibres, resulting in fibrosis. Anti-nuclear antibodies and anti-centromere antibodies are raised in this condition. The lower oesophagus is often affected, resulting in poor peristalsis, severe GORD with stricture formation and Barrett's oesophagus.

Systemic lupus erythematosis

Systemic lupus erythematosus (SLE) is a progressive systemic inflammatory disease involving skin, joints and internal organs that can affect the oesophagus and can cause oral mucosal ulcerations. The dysphagia tends to be mild.

Dermatomyositis

Dermatomyositis is a diffuse inflammatory condition affecting skin and skeletal muscle associated with underlying malignancy in a high percentage of patients. Dysphagia is seen in up to a third of affected patients and may be secondary to hypopharyngeal and upper oesophageal involvement. It usually presents with symmetrical proximal muscle weakness and skin changes. Diagnosis is made by a muscle biopsy.

Pemphigus, mucosal pemphigoid and epidermolysis bullosa

These conditions are characterized by blistering, either subepidermal (pemphigus) or submucosal (mucosal pemphigoid and epidermolysis bullosa). The oral cavity, pharynx and oesophagus can be involved, leading to scarring and stricture. Diagnosis is made by skin biopsy showing typical antibodies with direct immunofluorescence. Contrast swallow can have a characteristic appearance. There is often a good response to steroids.

Sjögren's disease

Sjögren's disease causes dysphagia due to xerostomia. Anti-Ro (SS-A) antibody levels are raised in 70% of cases and anti-La (SS-B) in 40%. However, a negative blood test does not exclude the condition. Biopsy of the minor salivary glands of the lip will show lymphocyte infiltration and aid the diagnosis.

Traumatic

FOREIGN BODY/FOOD BOLUS OBSTRUCTION

A foreign body in the pharynx or oesophagus is the most common traumatic cause of dysphagia. Patients often present with accompanying drooling. It is important from the history to determine whether it is a sharp foreign body or a soft food bolus obstruction.

A variety of foreign bodies are ingested by children and patients with learning difficulties, the most common being coins. The size and shape of the foreign body will dictate where it lodges, but common sites are the cricopharyngeus, at the level of the aortic arch and at the cardia.

Food bolus obstruction from large pieces of meat (with or without bone) is not uncommon, particularly in those who cannot or do not chew well and in patients with oesophageal stricture. Patients present with painful dysphagia and, if obstruction is complete, there will be drooling of saliva. Laryngoscopy may confirm pooling of saliva. Neck examination may reveal subcutaneous emphysema if pharyngeal or oesophageal perforation has occurred. A lateral soft-tissue radiograph of the neck shows loss of natural lordosis of the C spine, widening of the prevertebral space and often an air bubble in the oesophagus. A radio-opaque foreign body may be seen. Urgent rigid or flexible endoscopy might be required if the foreign body does not pass spontaneously and with sharp foreign bodies. If perforation is suspected, it may be necessary to perform a contrast swallow with a non-ionic contrast, which has the added advantage of not interfering with subsequent oesophagoscopy as it is clear.

CAUSTIC BURNS

Burns due to accidental or deliberate ingestion of acid or alkaline substances cause dysphagia. Initial oedema and ulceration can result in stricture formation and perforation.

HEAD, NECK AND SPINAL TRAUMA

Trauma to the head and neck, chest or cervical spine may be accidental or iatrogenic and may involve blunt trauma, penetrating injuries or compression effects or

a combination of these. Neck injuries may disrupt the swallowing mechanism directly or indirectly by affecting the cranial nerves IX to XII. This is discussed in greater detail in Chapter 38, Neck trauma. Head injuries can produce a variety of neurological defects resulting in paresis, paralysis or loss of coordination of the swallowing mechanism, which may not become apparent until the patient resumes consciousness, starts feeding again and aspiration results.

Neoplastic

Both benign and malignant tumours may cause dysphagia either by mechanical obstruction, intra- or extraluminal, or due to neuromuscular invasion. A number of studies have shown that the severity of dysphagia and its complications depend on tumour size and site.[14–20] One study showed that 50.9% of patients with pharyngeal tumours had dysphagia at presentation compared with 28.6% of patients with laryngeal tumours and 28.2% with oral lesions of stage T2 or more.

In the oral cavity, most tumours are malignant and of these 95% are squamous cell carcinomas (SCCs). The patient may present with a lump in the mouth or with an ulcer that may result in odynophagia. Dysphagia can be caused by tongue fixation. In the oropharynx, most malignant tumours are squamous cell in origin. Dysphagia is often due to pain but involvement of the tongue base and/or soft palate can result in problems with tongue fixation and regurgitation respectively. The tumour is often seen on examination. In the hypopharynx, rare benign tumours such as leiomyomas, lipomas and fibrolipomas can be found which cause dysphagia. The majority of tumours, however, are SCCs, with 60% occurring in the piriform fossa. Large tumours can cause significant swallowing problems with alteration of diet to softer textures. Weight loss is not uncommon and symptoms of aspiration such as cough associated with swallow and recurrent chest infections should be asked about. Small tumours and tumours of the postcricoid region or the cervical oesophagus can be more difficult to diagnose. The patient may only complain of a feeling of 'something in the throat', like a crumb being stuck. At examination it is important to look for pooling of saliva and any localized oedema, which might raise suspicion. In cases where there is a high index of suspicion or an obvious tumour, an assessment of the upper aerodigestive tract (UADT) and staging of the tumour is made, usually under general anaesthetic. Cross-sectional imaging MRI or CT is also helpful.

In the oesophagus, benign leimyomas can be found occasionally but the majority of tumours are squamous carcinomas. Adenocarcinomas may develop at the lower end and may arise from gastric metaplasia, as seen in Barrett's oesophagus. Dysphagia of short duration in an elderly male who smokes and drinks and which progresses from solids to liquids is typical for this type of tumour. Examination may show weight loss and anaemia and cervical lymphadenopathy advanced disease, but there may be little to find in early disease. Oesophageal lesions are best dealt with within the upper gastrointestinal multidisciplinary team and investigated with flexible gastroscopy and cross-sectional imaging.

External compression of the oesophagus due to goitre and thyroid malignancies, thymoma and enlargement of mediastinal lymph nodes, seen in metastatic disease and lymphoma, is not uncommon and investigations primarily involve cross-sectional imaging and tissue diagnosis.

Post-treatment dysphagia

Patients who have undergone treatment for HNC often suffer significant dysphagia and aspiration. Longer oral and pharyngeal transit times, greater amounts of oral and pharyngeal residue, shorter cricopharyngeal opening durations, and poor swallow efficiencies are seen. Swallow function is significantly worse with higher tumour stage, and patients with oral or pharyngeal lesions have worse swallow function than patients with laryngeal lesions.[20, 21] A multicentre study found a much higher proportion of HNC patients aspirated (76%) than did patients with neurogenic, medical, gastrointestinal diseases.[4] These effects are long-standing, with one study reporting that 44% aspirated at 5 years and beyond their original treatment.[22]

Chemoradiotherapy is, in many centres, the standard treatment for locoregional advanced tumours, particularly of the oropharynx, larynx and hypopharynx. Despite the encouraging results in terms of locoregional control and survival, significant functional impairment has been documented. This is discussed in greater detail in Chapter 34, Speech voice and swallow rehabilitation after chemoradiation, but the salient points are covered here.

Common problems include: reduced tongue strength and control, decreased tongue base movement towards the posterior pharyngeal wall, decreased laryngeal elevation, reduced epiglottic inversion, delayed pharyngeal swallow, frequent residue in vallecula and piriform sinuses and frequent penetration of the laryngeal vestibule and frank aspiration.[23] A prospective study found that 30% of HNC patients treated by chemoradiotherapy developed aspiration pneumonia, despite being fed by tube.[24]

The radiation dose delivered to the superior and middle pharyngeal constrictors, longitudinal muscles and palatopharyngeal fold appears to be significantly related to swallowing outcomes.[25] Intensity-modulated radiotherapy (IMRT) is designed to reduce doses to the major salivary glands, constrictor and masticatory muscles and the mandible. While studies have demonstrated improved salivary function,[26] swallowing function is not always improved.[27] This may be because it is impossible to spare key structures such as the tongue base and soft palate due to tumour site. The pharyngeal phase of swallowing depends on precise interaction of these muscles with tongue base movement, pharyngeal contraction and hyolaryngeal excursion. Gastric tube dependence has been noted for 13–33% at long-term follow-up after chemoradiation.[24]

These problems can also occur following surgery, but are perhaps more predictable. Reconstruction using

regional and microvascular flaps along with rehabilitative therapy has been shown to be beneficial, allowing some compensation.[28, 29] A shift in surgical techniques towards transoral resections involving the use of the laser and the robot have resulted in reduced anatomical and functional disruption and in improved swallowing outcomes, even when radiotherapy and chemotherapy are used in the adjuvant setting.[30, 31]

Functional endoscopic evaluation of swallowing (FEES) is very helpful in the post-treatment HNC patient and is easily performed in the outpatient clinic setting. A functional evaluation including a pharyngeal squeeze manoeuvre,[32] forced breath hold, maintenance of glottic closure and dry swallow can be made and a range of fluid and food can be given. Food colouring can be added to improve the view. Bolus flow during swallow, laryngeal penetration and aspiration and pre- and post-swallow residue in the vallecullae, piriform fossa and postcricoid area should be documented.

Oesophageal motility disorders

These disorders can produce severe dysphagia in the absence of visible abnormalities, the diagnosis being made by manometry.[33] However, before the diagnosis of a dysmotility disorder is made, it is important to exclude a tumour or structural abnormality by endoscopy or radiology.

ACHALASIA CARDIA

Achalasia cardia is the classical condition in this group wherein the lower oesophageal sphincter fails to relax and allow food to pass into the stomach. It is caused by degeneration or absence of the ganglion cells (myenteric plexus of Auerbach) in the oesophageal wall. The condition is indistinguishable from Chagas disease, seen in patients from South America and due to infection by *Trypanosoma cruzi,* which destroys the ganglion cells. Patients present with difficulty in swallowing fluids initially and progressively difficulty with solids. Barium swallow will demonstrate a 'bird's beak' tapering on the oesophagogastric junction and dilatation of the lumen above it. Manometry studies can be used to detect failure of the lower oesophageal sphincter to open even before the features on barium swallow appear.

OESOPHAGEAL SPASM

Diffuse oesophageal spasm is a condition characterized by non-effective peristaltic waves of high amplitude in the oesophagus, causing angina-like chest pain. Barium swallow and manometry demonstrate non-propulsive peristaltic waves and incomplete lower oesophageal sphincter relaxation.

PRESBYDYSPHAGIA

Presbydysphagia refers to swallowing difficulties due to ageing which affect all stages of swallowing. The oral phase is affected by loss of teeth and tongue connective tissue, reduced strength of mastication and weakness of the velopharyngeal reflexes. The pharyngeal phase is affected by decreased elevation of the larynx and prolongation of the pharyngeal transit time. In the oesophageal stage, there is prolongation of the upper oesophageal sphincter relaxation time and the oesophageal transit time with ineffective tertiary peristaltic waves. However, these age-related changes and abnormalities, seen on barium swallow, are evident in one-third of otherwise healthy elderly individuals. Therefore, it might be that age-related changes reduce functional reserve such that problems develop more easily when disease or generalized weakness from systemic illness ensues.[34]

Neurological

Neurological causes of dysphagia[35] mostly affect the oropharyngeal phase of swallowing. Usually, the motor, sensory and coordinating centres for swallowing are affected directly by the disease and it is unlikely that the dysphagia would present as an isolated symptom without the other characteristic features of the neurological disease. In general, patients who present with an acute disorder causing dysphagia, such as a stroke, tend to improve with time, whereas patients with chronic neurological disorders will experience progressive swallowing difficulties. Diagnosis of the specific swallowing problem in these conditions is made by a careful assessment including a detailed head and neck examination. Speech and swallowing assessments include water swallow test to help screen for risk of aspiration and VF. Constant re-evaluation is often needed.

CEREBROVASCULAR ACCIDENT (STROKE)

Cerebrovascular accident (stroke) is probably the most common neurological disorder causing Dysphagia, by affecting the cortex or the corticobulbar tracts (pseudobulbar palsy) or by affecting the bulbar nerve nuclei (bulbar palsy). Recovery takes place within the first week in the majority of patients. Factors contributing to the dysphagia include delayed triggering of the swallowing reflex, cricopharyngeal dysfunction and reduced tongue control and pharyngeal contraction and cough. Loss of pharyngeal sensation associated with the dysphagia correlates well with aspiration, aspiration pneumonia being a major cause of death after a stroke. Following a stroke, studies suggest that 25–70% of patients have dysphagia initially, with 10–30% continuing to have dysphagia and aspiration even after recovery.[1, 2]

PARKINSON'S DISEASE

Parkinson's disease is progressive and characterized by the triad of resting tremor, bradykinesia and rigidity, patients having difficulty in starting, performing and stopping a movement. The dysphagia is associated with changes in striated muscle under dopaminergic control and smooth muscle under autonomic control and is mostly due to

abnormalities in the oral preparatory and pharyngeal phases of swallowing. The oral phase of the swallow is affected by rigidity of the tongue musculature with inefficient, non-propulsive, back and forth movement of tongue which prevents food being delivered into the oropharynx. In the pharyngeal phase there is delayed contraction of the pharyngeal muscles. Findings on VF include impaired motility, hypopharyngeal stasis, aspiration and poor movement of the epiglottis.

MULTIPLE SCLEROSIS

Multiple sclerosis is a demyelinating disease affecting the brain and spinal cord. There can be either a relapsing–remitting or a progressive course. Swallowing problems and aspiration tend to occur in end-stage disease in up to a third of the patients. Reduced pharyngeal peristalsis and delayed swallowing reflex are the most common features. However, the demyelinating lesions can occur in a single cranial nerve or cause a general dysfunction of all three phases of deglutition.

MOTOR NEURONE DISEASE

Motor neurone disease (amyotrophic lateral sclerosis) is a progressive disease that affects the corticobulbar and corticospinal tracts. Progressive swallowing difficulties affect mainly the oral and oropharyngeal stage of swallowing. Twenty-five per cent of patients present with swallowing problems and most develop problems as the disease progresses. Swallowing problems together with dysarthria and anarthria account for much of the misery of this disease.

MYASTHENIA GRAVIS

In myasthenia gravis there are antibodies to acetylcholine receptors, impairing the function of the neuromuscular junction of striated muscles. The hallmark of this condition is fatigability. There is bulbar muscle weakness manifested by slow and weak tongue movements, fatigue of swallowing and food residue in the oropharynx. There may be laryngeal penetration and aspiration. The diagnosis is a clinical one supported by the presence of acetylcholine receptor antibodies

RECURRENT LARYNGEAL NERVE PALSY

Isolated recurrent laryngeal nerve palsy can be associated with dysphagia and aspiration of liquids due to decreased pharyngeal gradient pressures and decreased glottic closure, as well as inferior constrictor and cricopharyngeus muscle dysfunction. Combined superior and recurrent laryngeal nerve injury will have a greater impact due to the ipsilateral sensory deficit.

Medication-induced/pharmacological

Drugs can cause dysphagia directly by causing oesophagitis, or as part of their pharmacological action or normal side effects.[36] Swallowing tablets with insufficient water or just before going to bed can cause oesophagitis as oesophageal transit time is longer during sleep. The oesophagus at the level of the aortic arch is most commonly injured by both lack of neutralization by saliva and contact by acid-producing drugs with a pH of less than 3, such as tetracyclines, doxycycline, vitamin C and ferrous sulphate. Broad-spectrum antibiotics and chemotherapeutic drugs may cause secondary viral ulceration or fungal infections. Stevens–Johnson syndrome is a more serious complication of antibiotic therapy with an acute erosive pharyngitis and oesophagitis causing dysphagia as well as delayed oesophageal strictures.

Anticholinergics, tricyclic antidepressants and calcium channel blockers decrease oesophageal peristalsis and tone of the lower oesophageal sphincter. Xerostomia is a common side effect of many medications such as antihypertensives, ACE-inhibitors, anticholinergics, antiemetics, antihistamines, diuretics and opiates.

Miscellaneous

GLOBUS PHARYNGEUS

Variously described as ‘foreign body sensation in the throat’, ‘lump in the throat’ and ‘frog in the throat’, globus sensation in the throat should not be associated with genuine dysphagia. This should be ascertained with a detailed and specific history from the patient. Investigations and management of this condition are discussed in Volume 2, Chapter 34, Foreign bodies in the ear, nose and throat. It is imperative to rule out a lesion in the hypopharynx, remembering especially not to miss an inconspicuous pathology in the postcricoid area. Similarly, a small group of patients with oesophageal malignancy may also present with this symptom.[37] Therefore, flexible nasendoscopy, transnasal oesophagoscopy and barium swallow tests should be used as appropriate in these patients.

PHARYNGEAL POUCH

A pharyngeal pouch is a pulsion diverticulum that occurs at an area of weakness between the two parts of the inferior constrictor at Killian’s dehiscence. The pouch first develops in the midline, but as it enlarges it expands to one side, most frequently the left. Manometric studies suggest that it is associated with high intrapharyngeal pressures with a high resting tone in cricopharyngeus that is slow to relax.[38] Patients first present with dysphagia and regurgitation of undigested food but recurrent chest infections can result from aspiration due to overflow of food into the larynx. Diagnosis is confirmed by a barium swallow. For more information on the aetiology and management of this condition, see Chapter 52, Cricopharyngeal dysphagia.

Box 49.1 lists the causes of dysphagia.

BOX 49.1 Causes of dysphagia

Congenital
- Cleft lip and palate
- Cerebral palsy
- Vascular rings
- Atresis, clefts and fistula
- Congenital vocal cord palsy

Infective
- Acute and chronic infections of pharynx/larynx
- Neck space infections

Inflammatory
- Gastro-oesophageal reflux disease
- Laryngopharyngeal reflux
- Patterson–Brown–Kelly syndrome
- Eosinophilic oesophagitis

Autoimmune
- Scleroderma
- Systemic lupus erythematosus
- Sjögren's syndrome
- Pemphigus, epidermolysis bullosa
- Dermatomyositis

Traumatic
- Foreign body
- Food bolus obstruction
- Caustic burns
- Head and neck trauma

Neoplastic
- Benign tumours
- Malignant tumours

Motility disorders
- Achalasia cardia
- Oesophageal spasm
- Presbyoesophagus

Neurological
- Cerebrovascular accident
- Parkinson's disease
- Multiple sclerosis
- Motor neurone disease
- Myasthenia gravis
- Vocal cord palsy

Miscellaneous
- Post-treatment dysphagia
- Pharmacological
- Globus pharyngeus
- Pharyngeal pouch

ASSESSMENT OF DYSPHAGIA AND ASPIRATION

Assessment of dysphagia typically includes both clinical and instrumental evaluation. **Figure 49.1** provides a suggested algorithm for the clinical assessment of dysphagia.

History

Patients complain of difficulty in swallowing food or liquid easily and there can be a sensation of food sticking. They will often localize the level of this sensation. In high (oropharyngeal) dysphagia, there is difficulty in preparing and transporting the food bolus through the oral cavity, as well as initiating the swallow, and this may be associated with aspiration or nasopharyngeal regurgitation. In low (oesophageal) dysphagia, patients complain of food sticking low in the neck, retrosternally or at the epigastrium. This localization has low diagnostic specificity. Around 30% of oesophageal dysphagia is localized above the suprasternal notch.

The history should include the onset, duration, progression and severity of the symptoms, as well as the types of food that give problems. Typically, malignant dysphagia presents with a short and progressive history, a change to softer textures and more liquid consistency, with associated weight loss. Conversely, in neuromyogenic dysphagia it can be more difficult to swallow fluids.[39]

Patients may complain of a number of other UADT symptoms:

- **Regurgitation**, which can be immediate or delayed, can give an indication as to the level of the problem. Delayed regurgitation of undigested food is typically seen in patients with a pharyngeal pouch.
- Symptoms of **retrosternal discomfort, belching and early satiety** indicate GORD.
- **Odynophagia** (pain on swallowing), is associated with infection, neoplasia or GORD.
- **Hoarseness** may indicate laryngeal fixation due to tumour or vocal cord palsy.
- **Choking or coughing**, during or after eating, or frequent chest infections may suggest aspiration.
- **Referred otalgia** via the IX and X cranial nerves is usually secondary to an UADT tumour and a poor prognostic sign.
- **Associated neurological symptoms** such as bulbar dysfunction, dysarthria, diplopia, limb weakness and fatigability can be seen in motor neurone disease and myasthenia gravis. Tremor, ataxia and unsteady gait are features of Parkinson's disease.

Examination

Examination should exclude any obvious structural cause, and assessment should be made for signs of associated systemic or neurological dysfunction and for signs of complications of dysphagia such as weight loss and malnutrition and pulmonary problems due to aspiration.

The oral cavity and oropharynx should be examined carefully, looking for obvious mucosal ulceration or lesions and oral dryness/xerostomia. Palatal raise and gag reflex and tongue movement are assessed and any wasting or fasciculation of the tongue noted. Asking the patient to say 'la' and 'ka' can assess anterior and posterior tongue elevation. Dentition and the presence and fit of dentures are assessed; oral competency and buccal tension can be confirmed by testing for facial nerve function.

The pharynx and larynx should be examined with flexible nasendoscopy, assessing for an UADT lesion, vocal cord mobility and pooling of saliva in the piriform fossa

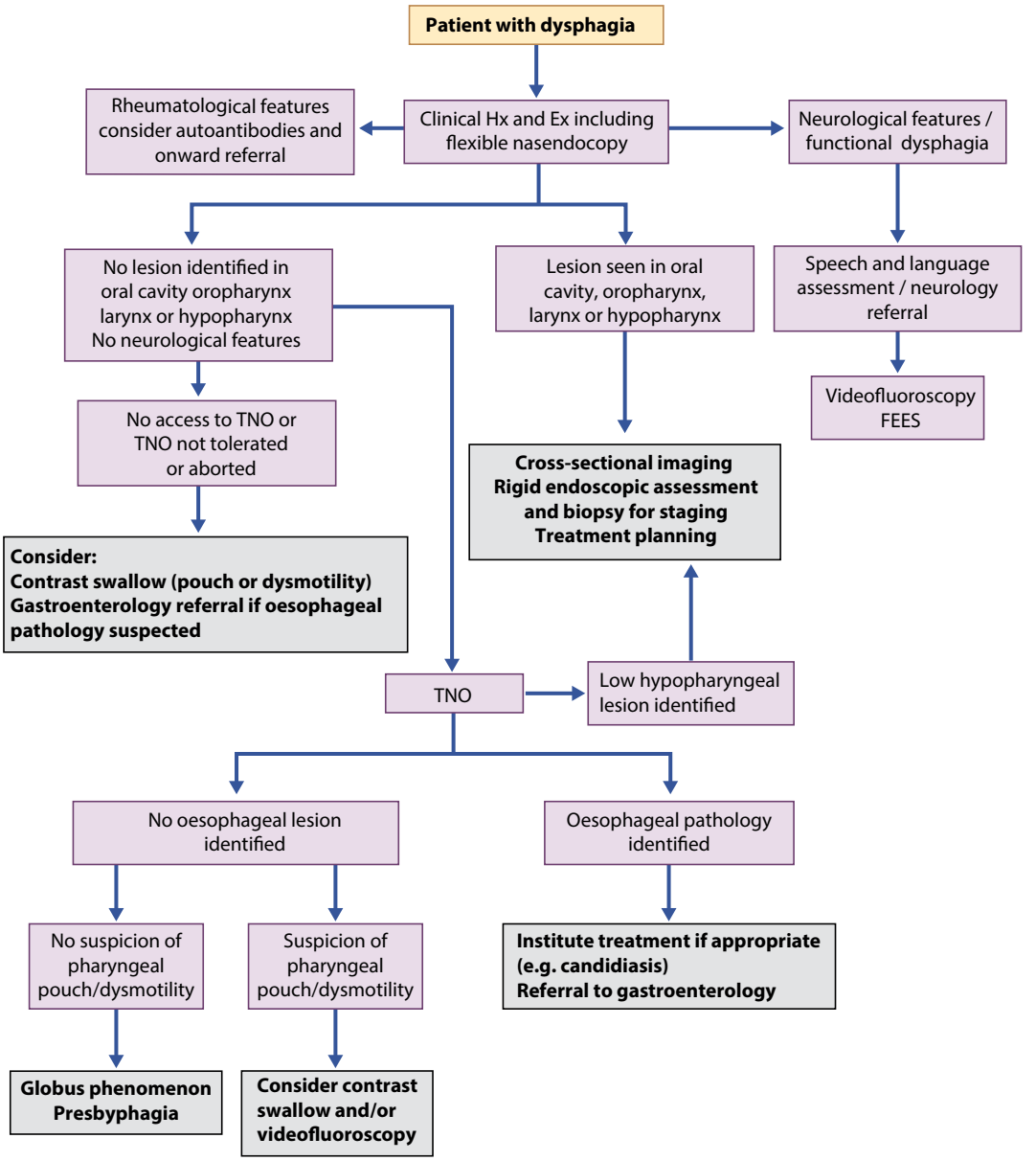

Figure 49.1 A suggested algorithm for clinical assessment of a patient with dysphagia. TNO, transnasal oesophagoscopy; FEES, fibre-optic endoscopic evaluation of swallowing.

or postcricoid area, which is suggestive of an organic cause of dysphagia. Where facilities are available, the flexible endoscopy should be performed using a transnasal oesophagoscope which will enable concurrent assessment of the larynx, pharynx and the entire oesophagus.

Lower cranial nerve function is assessed for loss of tongue movement, wasting and fasciculation, loss of gag and cough reflexes, loss of pharyngeal and laryngeal sensation and loss of vocal cord mobility.

The neck is examined for lymphadenopathy and other neck masses, thyroid enlargement, loss of laryngeal crepitus and the integrity of the laryngeal cartilages.

General physical and neurology examinations should look for evidence of malnutrition, weight loss, chest disease, epigastric tenderness and abdominal swellings, loss of coordination, fasciculation and tremor.

Investigations

Clinical findings dictate further investigations. In the case of upper UADT lesions, investigation is to assess and stage the tumour with panendoscopy and cross-sectional imaging. However, history and examination may not reveal the cause of dysphagia though it may suggest that the cause is either lower than the hypopharynx or has a neurological or functional basis. Further investigations aid examination and assess the function of the swallowing pathway and are also used to assess the risk of aspiration.

BLOOD TESTS

A full blood count and indices should be obtained in all patients to exclude anaemia as a cause or effect of

the dysphagia. Liver and renal function tests together with serum calcium levels should be acquired when nutrition is impaired or metastases are suspected. Thyroid function tests are indicated if dysphagia is caused by a goitre or thyroid malignancy. Creatine kinase levels may be elevated in myopathies.

BEDSIDE ASSESSMENTS

Bedside assessments of swallowing are not standardized and offer poor reliability when used alone. A water swallow test (WST) of a defined volume of water (30 mL) and looking for abnormal voluntary cough, post-swallow cough or throat clear or voice has been shown to have about a 50% sensitivity for aspiration and 80–92% specificity.[40–42] It is used to screen patients with neurological dysphagia at risk of aspiration and is a useful adjunct to instrumental testing.[43] In the HNC population, WST using 100 mL has been found to be 67% sensitive for aspiration but less specific (46%).[20] The value of WST is in identifying patients who require instrumental testing.

Evan's blue dye test[44, 45] is used to assess the presence of and aspiration in the tracheostomized patient. The presence of blue dye from the tracheostomy site is assessed after a test swallow. Detailed treatment of swallow assessment can be seen in Chapter 50, Functional investigations of the upper gastrointestinal tract.

QUESTIONNAIRE-BASED ASSESSMENTS

There are a number of self-reported (University of Washington Quality of Life,[46] M.D. Anderson Dysphagia Inventory[47] and SWAL-QOL[48]) and observer-rated questionnaires that can be useful adjuncts in the assessment of dysphagia in the head and neck population. The most used observer-rated instrument is the Performance Status Scale for Head and Neck (PSSHN).[49] Swallow performance is assessed by: (i) eating in public (scale 1–5) and (ii) normalcy of diet (scale 1–10). These instruments are discussed in greater detail in Chapter 28, Measures of treatment outcomes.

INSTRUMENTAL TESTING

Fibre-optic endoscopic evaluation of swallowing

A fibre-optic endoscopic examination of the UADT should be performed in all cases of dysphagia. The assessment of swallow (fibre-optic endoscopic evaluation of swallowing – FEES)[50, 51] as part of this is very useful in identifying aspiration and secretion management and for visual biofeedback for the patient when trying compensatory procedures to aid swallowing and reduce aspiration. This test can be performed at the bedside and is best if a digital recording is made. Different textures of foodstuffs can be given which can be dyed with food colouring to enhance visibility. Bolus flow during swallow, laryngeal penetration and aspiration, and post-swallow residue should be documented. Endolaryngeal sensation can also be assessed. The procedure is described fully in Chapter 50, Functional investigations of the upper gastrointestinal tract.

Direct pharyngo-oesophagoscopy

This is an examination to visualize and biopsy the pharynx and upper oesophagus under general anaesthetic. It is performed to biopsy and stage all cases of UADT tumour and in patients who complain of food sticking. It allows inspection of the postcricoid area, which is not seen so well during flexible endoscopic assessment of the upper gastrointestinal tract. It is used to examine pharyngeal pouches and to facilitate their treatment.

A major drawback of this assessment technique is the need for a general anaesthetic. In the UK, use of the rigid endoscope to examine the lower one-third of the oesophagus is discouraged owing to the higher risk of complications.

Gastroscopy

Gastroscopy (or oesophagogastroduodenoscopy – OGD) is the endoscopic examination of the oesophagus and stomach. It is used to assess, stage and biopsy oesophagitis, Barrett's oesophagus and tumours. It is poor at detecting disease of the hypopharynx.

Transnasal oesophagoscopy

The relatively new technique of transnasal oesophagoscopy (TNO)[52] uses a narrow-bore flexible scope to assess the oesophagus under local anaesthetic in the clinic setting. It has been shown to be reliable at assessing and diagnosing oesophageal pathology. Studies have shown that around 40% of patients being referred to otolaryngologists with swallowing problems can have concurrent oesophageal pathology, justifying inclusion of this procedure as one of the investigative options for dysphagia.

The major clinical advantage of TNO is the lack of sedation-related morbidity and mortality that is associated with OGD under sedation. It is also more cost-effective than OGD.

Manometry

This is the measurement of oesophageal pressures at rest and during swallowing to diagnose motility disorders.[53] A catheter with pressure transducers along its length is placed in the oesophagus and a multichannel system records the contraction amplitude, duration, coordination and velocity of each peristaltic wave. It is particularly helpful in patients with atypical chest pain and unexplained causes of dysphagia. Conditions with almost pathognomonic manometric findings include achalasia, diffuse oesophageal spasm and scleroderma.

Twenty-four hour ambulatory oesophageal pH monitoring

This is regarded as the most accurate method of diagnosing GORD.[53] It is especially useful when standard investigations such as flexible oesophagoscopy and barium swallow (see below) are normal in a patient with typical symptoms, or in patients with atypical symptoms. A pH sensor placed 5 cm above the manometrically defined lower oesophageal sphincter continually monitors the pH over the test period, while the patient records their symptoms, mealtimes, going to bed and getting up in a

diary card or with an event marker on the pH recorder. Normal oesophageal pH varies between 5 and 7 and GORD is present when the pH is less than 4. The results are expressed as the percentage of time the pH is less than 4 over a 24-hour period – the DeMeester score.[54]

RADIOLOGICAL INVESTIGATIONS

There are two radiological assessments of swallowing that are important in the assessment of dysphagia: contrast swallow and VF.

Contrast swallow

The traditional barium swallow includes both static and dynamic assessment of swallow. The patient is given a cup of liquid barium to swallow and the bolus is followed fluoroscopically to the stomach. Improved visualization of mucosal detail can be obtained by using effervescent granules of barium producing an air contrast study. It is useful to diagnose intrinsic disease (diverticulae, stricture or web, tumour and dysmotility) and extrinsic disease (compression from thyroid or cervical osteophytes). It has poor sensitivity for other pharyngeal disease. It may show reflux disease, but it is not a very sensitive as it fails to pick up 40% of cases.[55] Oesophageal motility is also assessed with swallows in different positions.

Tertiary and disordered contractions can be seen – these patients not uncommonly present with pharyngeal symptoms. The use of barium is contraindicated when there is a risk of aspiration since it can cause pneumonitis. Urgent physiotherapy is necessary in cases of aspiration. In these situations a low molecular weight, non-ionic, water-soluble contrast medium should be used as this is less irritant and should cause minimal complications.

Videofluoroscopy (VF)

VF is a true dynamic assessment of swallowing and is considered to be the gold standard for evaluating the swallowing mechanism.[56] The passage of measured volumes and viscosities – liquid, puréed and solid foods – is observed in both the lateral and anteroposterior plane and a recorded study made. It is a comprehensive test for all phases of swallowing but particularly useful for the oral and pharyngeal phases. The study is interpreted and assessment made of bolus preparation and propulsion. If detected, aspiration can be measured on scales such as the penetration–aspiration scale.[57] Manoeuvres can be tested to reduce aspiration, including swallowing during breath-holding, with or without a chin tuck, and with or without a head turn towards the affected side. VF is particularly useful in patients with neurological disease, and in patients after treatment for HNC.

Computed tomography

Patients with malignant dysphagia should have a CT examination of the neck, chest and abdomen to stage their disease, as should those with dysphagia due to extrinsic compression.

Magnetic resonance imaging

Magnetic resonance imaging (MRI) of the brain or skull base is indicated when a neurological cause of dysphagia is suspected such as multiple sclerosis, cerebral tumours and intracranial extension of a nasopharyngeal carcinoma. It is particularly useful for lesions around the foramen magnum and the brainstem. It is also used to diagnose vascular anomalies.

BEST CLINICAL PRACTICE

- ✓ Be aware of the wide and varied causes of dysphagia in adults and children.
- ✓ Take a detailed current and past medical history to provide clues as the possible aetiology.
- ✓ Comprehensively examine the H&N including the lower cranial nerves.
- ✓ A fibre-optic endoscopic examination of the UADT should be performed in all cases of dysphagia .
- ✓ Look for signs of malnutrition.
- ✓ Perform FBC in all patients with dysphagia.
- ✓ Consider TNO where there is access to this.
- ✓ Consider instrumental assessment of swallowing – FEES and VFSS.
- ✓ Where there is a concern of a malignant cause arrange cross-sectional imaging and UADT assessment under general anaesthetic.
- ✓ Consider a BaSw in cases of pharyngeal pouch and dysmotility.

KEY POINTS

- Dysphagia is common: 22% of over individuals over 50 are affected.[1,2]
- Aspiration pneumonia is the highest cause of mortality associated with hospital admission.[7]
- Stroke is the commonest neurological cause of dysphagia and aspiration.[1, 2]
- 76% of HNC patients have been shown to aspirate. This is higher than those with medical, neurological or GI problems.[4]
- VFSS is considered the gold standard for evaluation of swallow and should be used in conjunction with FEES.[56]
- 30% of patients treated with CRT develop aspiration pneumonia despite tube feeding.[24]
- Radiation dose to the superior and middle constrictor is significantly related to swallow outcome.[25]
- Laryngeal signs show poor sensitivity and specificity for LPR.[10]

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CHAPTER 50

FUNCTIONAL INVESTIGATIONS OF THE UPPER GASTROINTESTINAL TRACT

Joanne M. Patterson and Jason Powell

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SEARCH STRATEGY

Data in this chapter are based on searches of Medline, EMBASE and the Cochrane Library using the keyword Dysphagia, focusing on upper GI functional investigations. The articles referenced by these authors were also reviewed. The data are supplemented by further searches of specialized books.

INTRODUCTION

This chapter seeks to describe functional investigations of the upper digestive tract. A full investigation usually requires multidisciplinary input involving an otolaryngologist, speech and language therapist, radiologist and gastroenterologist, and a focused diagnostic examination with appropriate selection of instrumental assessment. The physiology of normal swallowing has been fully described in Chapter 48, Physiology of swallowing. The underlying aetiology for dysphagia is of anatomical, neurological, muscular or psychological origins. Early diagnosis and effective management of dysphagia reduce the incidence of pneumonia and improve quality of care and outcomes.[1]

INVESTIGATIONS

When to refer for a swallow assessment

Referral guidelines for swallowing assessments have been published for specific conditions. For example, patients with acute stroke should have a swallowing screening test, conducted by a trained healthcare professional before administrating any food, fluid or medication.[1] If a problem is identified, a specialist swallowing assessment should follow within 72 hours. Head and neck cancer patients referred for treatment that will affect swallowing should be assessed by a speech and language therapist and a plan for method of feeding devised.[2] As well as specific conditions, there are certain risk factors that require consideration. For example, a referral for a swallowing assessment is indicated for a tracheostomized patient if there is co-occurring neurological involvement following head and neck surgery, or there are signs of a problem such as evidence of secretions or ingested material on suctioning.[3] However, not all patients with a tracheostomy will have dysphagia.

Patients' perceptions of their swallowing do not always relate to function and therefore symptoms can be underreported.[4] The person may not be aware of a swallowing difficulty, or may attribute their problem to something else. Therefore, healthcare professionals need to be vigilant to the signs and symptoms, taking into account some of the more covert features and refer on for a specialist swallowing assessment as indicated. Some of the signs and symptoms of dysphagia include: coughing during or after eating and drinking, wet-sounding voice after eating and drinking, drooling, repeated chest infections, weight loss and dehydration.

Clinical swallowing evaluation

A clinical swallowing evaluation (CSE) is usually the first step in a functional assessment of the digestive tract and is primarily a screening assessment. The purpose is to identify and differentiate dysphagia symptoms, to assess severity and form a hypothesis regarding the underlying

anatomical and/or physiological causes. Swallow physiology cannot be directly observed if the breakdown is at the pharyngeal or laryngeal level. Sensory changes can mask any outward signs of difficulty such as coughing on swallowing. A CSE typically involves a detailed case history including relevant risk factors such as respiratory status and oral hygiene, an oropharyngeal and oromotor examination and an observation of a swallowing trial.

Currently, there are no published, standardized tests for a CSE. They have been criticized for their poor reliability and sensitivity when used in isolation. Reliability increases with the inclusion of a water swallow test (WST).[2, 3] Testing with measured amounts of water is more reliable than using trial water swallows,[5] probably due to a more defined pass or failed criterion. For example, a systematic review reported that a 30 mL WST could predict pneumonia in a hospital geriatric unit.[6] A combination of features identified on the oropharyngeal examination further increases the sensitivity for the detection of aspiration. For example, the presence of any two features from abnormal voluntary cough, absent gag reflex, dysarthria, dysphonia, post-swallow cough, throat clear or voice change improves validity over single items (sensitivity 92%, specificity 67%) in determining aspiration risk.[7]

A CSE may not be appropriate for certain populations, including patients with dementia or profound learning disability. For such groups, one may be limited to systematic observations of mealtime behaviours. Observations may include specific eating problems such as drooling or food pocketing, ability to self-feed, caregiver feeding skills, body and head positioning, behavioural issues such as agitation, sensory problems such as visual perceptual disorders and distraction by other stimuli. A systematic review of assessment tools for mealtime observations[8] identified two instruments with acceptable psychometric properties; the Minimal-Eating Observation Form-version II[9] and the McGill Ingestive Skills Assessment.[10]

A CSE may also include non-imaging equipment such as cervical auscultation, a cough response test using nebulized citric acid[11] and pulse oximetry. Cervical auscultation amplifies the sounds associated with breathing and swallowing. The flat diaphragm of a stethoscope is placed on the side of the thyroid cartilage. Several acoustic features of the swallow are noted, such as the release of subglottic air and epiglottic movement. There is disagreement over which sound or silent interval corresponds to which feature.[12–14] Swallowing sounds can be influenced by bolus volume and fluid viscosity.[15, 16] Furthermore, it appears that only a proportion of clinicians can achieve high inter- and intra-rater reliability.[12, 17]

Pulse oximetry measures oxygen desaturation. The intricacies of the respiratory–swallow cycle are described in Chapter 48, Physiology of swallowing. Aspiration of material can interrupt this cycle, impacting on arterial blood oxygenation. When used as part of a CSE, baseline measures need to be taken over a sufficient period of time and monitored for any changes following swallowing trials.[6] The sensitivity and specificity for pulse oximetry in identifying aspiration in the stroke population is questionable.[18]

Poor performance or uncertainty based on a CSE will influence the decision to perform a more in-depth, instrumental assessment.

When to refer for an imaging swallowing assessment

Screening assessments aim to identify whether someone has dysphagia, but cannot identify why the dysphagia is occurring. Instrumental tests have an important role in the identification of risk and safe management of aspiration, planning targeted interventions and provide outcomes on the effectiveness of treatment. The American Speech and Hearing Association (ASHA) and the Royal College of Speech & Language Therapists (RCSLT) have published guidelines on the conduct of instrumental swallowing assessments.[19, 20] ASHA's suggested criteria on when a swallow imaging assessment is indicated for assisting in making a diagnosis and/or planning dysphagia management include the following:

- The patient's signs and symptoms are inconsistent with the CSE findings.
- There is a need to confirm a suspected medical diagnosis and/or assist in the determination of a differential medical diagnosis.
- There is either nutritional or pulmonary compromise or a question of whether the oropharyngeal dysphagia is contributing to these conditions.
- Safety and efficiency of the swallow remain a concern.
- The patient is identified as a swallow rehabilitation candidate and specific information is needed to guide management and treatment.

An instrumental examination may be indicated for making the diagnosis and/or planning effective treatment in patients with suspected dysphagia based on the clinical examination and the presence of one or more of the following:

- The patient has a medical condition or diagnosis associated with a high risk for dysphagia, including but not limited to neurologic, pulmonary or cardiopulmonary, gastrointestinal problems; immune system compromise; surgery and/or radiotherapy to the head and neck; and craniofacial abnormalities.
- The patient has a previously diagnosed dysphagia and a change in swallow function is suspected.
- The patient has a communication or cognitive problem and is unable to complete a CSE.
- The patient has a chronic degenerative disease or a disease with a known progression, or is in a stable or recovering condition for which oropharyngeal function may require further assessment for management.

RADIOLOGICAL ASSESSMENTS OF SWALLOWING

There are two distinctly different barium swallows available for the evaluation of dysphagia: the traditional

barium swallow, and videofluoroscopy (also called a modified barium swallow or dynamic swallowing study). Logemann[21] published one of the first articles to describe a videofluoroscopic swallowing study (VFSS) as a diagnostic procedure for oropharyngeal dysphagia.

Videofluoroscopic swallowing study

A VFSS is a recorded radiographic study of the swallowing structures, their movement and coordination. Unlike a barium swallow, it is a dynamic assessment of swallowing. It tracks a radio-opaque bolus from the oral cavity to the upper oesophagus in the lateral or anterior–posterior plane and for this reason it has been deemed the 'gold standard' swallowing assessment. The examination typically involves a speech and language therapist, radiologist and/or radiographer. The presence of a radiologist is considered best practice for paediatric VFSS.[20] Other professionals who may be involved include physicians, surgeons, nurses, physiotherapists and occupational therapists. Specific referral procedures will vary according to local guidelines. Referring sources may include medical practitioners and designated referring speech and language therapists (SLTs). Patients must undergo an appropriate CSE prior to VFSS being undertaken in order to determine suitability and to direct the content of the examination.

PROCEDURE

Patients are not required to fast prior to a VFSS. Where possible, they should be positioned in their usual eating/drinking position. Test boluses are mixed with radio-opaque material to enable visualization. Consideration needs to be given to rheological characteristics, visibility and adherence or coating when adding substances such as barium. Guidelines for mixing the different commercially available radio-opaque substances are available from www.SteeleSwallowingLab.ca.[22, 23]

A VFSS should be systematic to allow for comparison within and between patients. Test boluses are given in increasing volume to minimize the risk of large amounts of aspiration. A range of different food textures may then be assessed, in a graded fashion. The majority of the VFSS is usually conducted in the lateral plane. An anterior–posterior view will give further information about symmetry of laryngopharyngeal movement and laterality of any residue. An oblique head position may be used to further investigate the upper oesophageal area. The number of test items will be limited in order to keep radiation dose to a minimum. The test may include a trial of compensatory strategies, for example an airway protection technique, a chin tuck position. These may then form part of an intervention plan.

Images are recorded digitally, for later analysis and interpretation. Patients may be shown the examination as part of shared decision-making and participation in management plans. If biomechanical movements are to be measured, a metal ring of known diameter (e.g. coin) is taped in the midline to the underside of the chin for calibration. Specific patient safety procedures need to be in place, i.e. access to suctioning in cases of gross aspiration as well as clinician safety guidelines for protection to radiation exposure.

CONTRAINDICATIONS AND RISKS

The examination is conducted in the radiology department and therefore patients need to be medically stable enough to attend and participate in the procedure. The referring clinician needs to consider whether the individual has the ability to cooperate with the examination, such as the ability to maintain the appropriate position and respond to instruction. Caution is needed when gross aspiration is suspected or where there is a history of respiratory distress/arrest due to aspiration. Patient pregnancy is another contraindication due to radiation exposure to the fetus. Needless to say, a VFSS cannot be performed on individuals who have been placed nil by mouth for reasons other than dysphagia (e.g. before general anaesthetic). Reports of adverse reactions to radio-opaque contrast are rare but could be life-threatening and therefore an alternative investigation needs to be found.

ANALYSIS

Interpretation of a VFSS includes a description of bolus flow, reactions to a misdirected bolus, presence of airway invasion, residue and variations from the normal anatomy and physiology. The rater considers the efficiency of bolus preparation and propulsion, and safety or airway protection. An analysis of oropharyngeal swallowing requires a thorough understanding of the normal swallow biomechanics in the context of influencing factors (i.e. gender, age). Typical anatomical abnormalities detected on VFSS include pouches, diverticulae, osteophytes, cricopharyngeal web and fistulae. A number of biomechanical measurements can be derived from the examination such as timing of swallow onset, hyolaryngeal movement, oropharyngeal movements, airway protection mechanisms, upper oesophageal opening. The presence of penetration, aspiration and residue and patients' response to it is recorded.

The reliability and validity of VFSS interpretation has been reported.[24–26] Reliability improves when examinations are group rated, viewed in slow time as well as real time, and judged using validated scales.[27, 28] Examples of rating scales include the MBSImps (a 17-point scale recording oropharyngeal swallowing impairment) and the penetration–aspiration scale (recording the depth of airway invasion and the patient's response to it).[27, 29, 30] Consideration needs to be given to the controlled nature of a VFSS and how much this reflects natural eating and drinking. Stability (i.e. the level of agreement between swallows of the same texture and volume) can vary between bolus consistencies. One study has demonstrated poorer stability for semi-solids than for liquids.[31] The clinician needs to integrate these findings when preparing the report, including recommendations for feeding and an intervention plan.

LIMITATIONS

There are several limitations of this assessment technique:

- Radiation exposure to the patient, especially for repeated or lengthy studies. However, 3 minutes of videofluoroscopy examination gives the equivalent radiation exposure as two cervical spine radiographs.[32] Scattered radiation exposure to the surroundings is within acceptable levels.[33]
- The cost of equipment and involvement of several specialist staff is high.
- There can be difficulties with positioning patients such as those who are bedbound or have difficulty with head control.
- The properties of barium are designed to coat structures, so liquid and food containing barium do not behave in the same way as normal liquids or food.
- Limited or inferred information only is gained about mucosa and secretions, sensation, inter-bolus pressure and glottic closure.

Barium swallow

The traditional barium swallow includes both static and dynamic components to identify intrinsic disease (tumours, diverticula, webs and dysmotility) and extrinsic disease (cervical osteophytes, enlarged thyroid gland). The oesophageal lumen is distended with liquid barium, or coated in thick barium and distended by gas to show intrinsic irregularities and extrinsic impressions. Static imaging with plain radiographs provides information on structural abnormalities (e.g. Zenker's diverticulum, cervical osteophytes), but these static images have little else to contribute to the investigation of dysphagia.[34]

Oesophageal motility is assessed with multiple single swallows in different positions, including recumbent (unlike in a videofluoroscopy assessment of oropharyngeal dysphagia), to assess peristalsis without the effect of gravity. Continuous and single swallows are observed separately as a second swallow obliterates peristalsis of the first.

If oropharyngeal dysphagia and aspiration are suspected, bolus sizes need to be kept small and the investigation should proceed cautiously, or a videofluoroscopy examination should be undertaken instead.

Both the oral and pharyngeal areas should be examined even if the complaint is only oesophageal as 35% of patients have simultaneous disorders of the pharynx and oesophagus[35] and the level of the lesion does not necessarily correspond to the site of the patient's symptoms.[36] Perlman et al.[35] give a comprehensive account of the interpretation of observations and dysphagic characteristics in the oesophageal stages of swallowing.

CT and MRI

These techniques both show structural lesions, for example intracranial disease causing neurogenic dysphagia.[37] More recently, high-speed MRI has been used for dynamic analysis of swallowing in both healthy volunteers and patients with dysphagia.[38, 39] MRI is a non-invasive test that gives both anatomical and functional information on swallowing that can be a useful addition to traditional assessment tools.[40] This technology is costly and still experimental and there is only limited published normal control data for comparison. These tests also require the participant to be supine while swallowing, which does not reflect normal swallowing activity.

ENDOSCOPIC EVALUATION OF SWALLOWING

Fibre-optic endoscopic evaluation of swallowing

A fibre-optic endoscopic evaluation of swallowing (FEES) affords a different perspective from a VFSS. It allows a direct view of nasolaryngopharyngeal anatomy and physiology, assessment of swallowing function and any compensatory interventions to facilitate swallowing performance.[41, 42] The equipment is portable so the test can be conducted at the bedside. This is particularly useful for vulnerable groups such as an intensive care unit setting. The endoscopic view can give specific information on secretion management (an important indication of aspiration),[43] the impact of fatigue (as the scope can be held in position for some time) and laryngopharyngeal sensation. Sensation may be measured quantitatively using FEES with sensory testing (FEESST), which requires additional equipment to deliver air pulses of differing intensity, duration and frequency through an additional port in the endoscope.[44] The patient can view their swallowing simultaneously, which is particularly useful for teaching swallowing manoeuvres.[45] The test may be conducted by an otolaryngologist and/or a trained SLT. In the latter case, any suspicious lesion, dysfunction or pathology needs to be referred back to the patient's medical team. Published guidelines are available from RCSLT[41] and ASHA.[46]

PROCEDURE

Patients are not required to fast prior to a FEES. They should be positioned in their usual eating/drinking position. First, the nostrils are examined using the tip of the scope to assess which side provides the wider access. Local anaesthesia is not routinely administered, to avoid desensitizing the pharyngeal or laryngeal mucosa. Topical anaesthesia or a decongestant may be applied to the nares only, for patients who have difficulty tolerating the procedure. The nasendoscope is coated in a water-based lubricant to ease its passage through the inferior meatus of the nasal passage. Four different views allow observation of anatomy and physiology during swallowing as follows:

- Nasal passage for elevation of the dorsal side of the velum (**Figure 50.1a**).

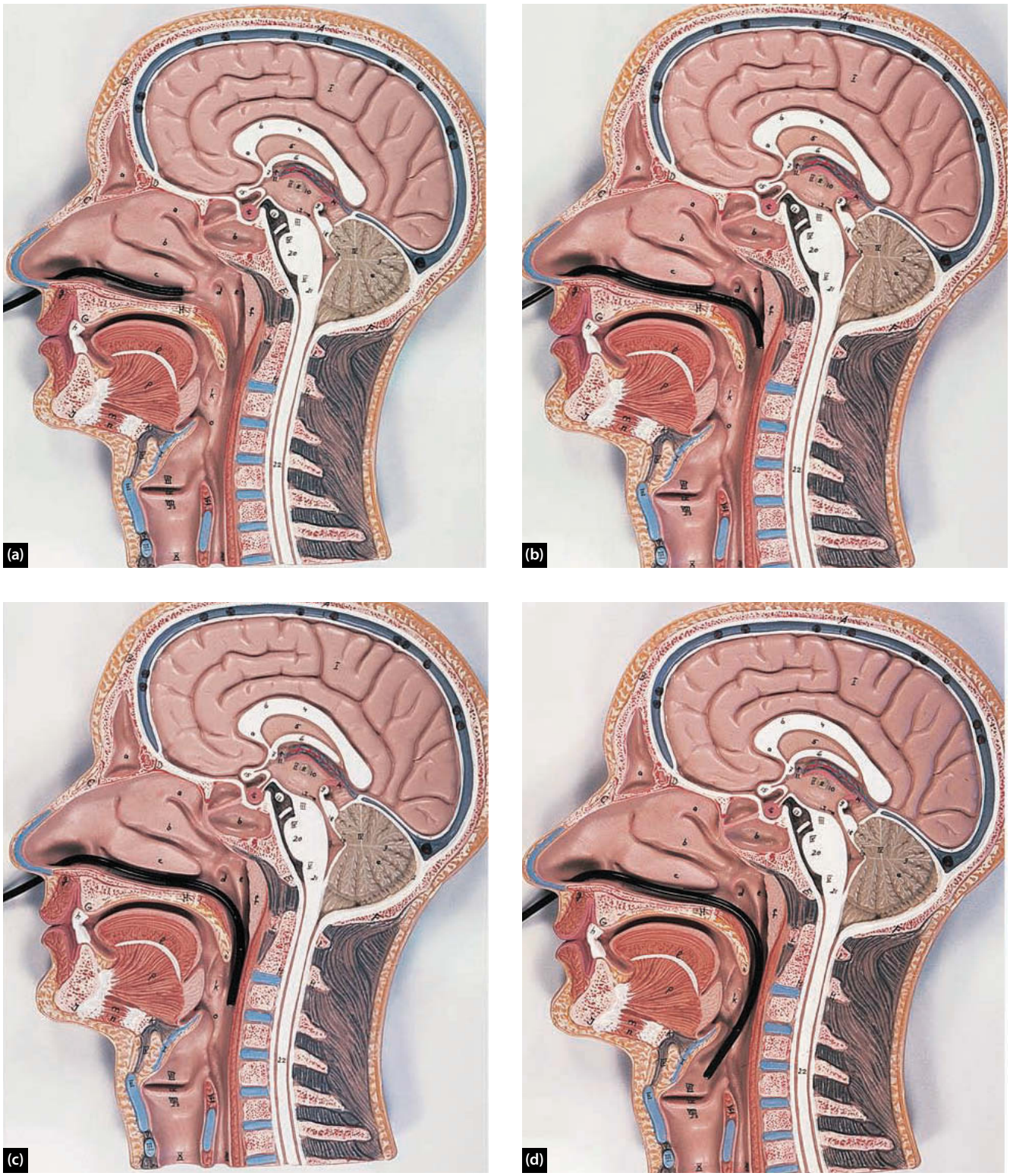

Figure 50.1 Endoscopic evaluation of swallowing. Nasendoscope positioned to view **(a)** dorsal side of velum, **(b)** nasopharynx, **(c)** oropharynx, and **(d)** hypopharynx/laryngopharynx.

- Nasopharynx for velopharyngeal competency, nasal reflux and lateral and posterior pharyngeal walls (**Figure 50.1b**).
- Oropharynx for base of tongue, epiglottis and larynx (**Figure 50.1c**).
- Hypopharynx for pyriform fossae, vocal folds and upper trachea (**Figure 50.1d**).

A functional evaluation is conducted prior to the introduction of any food or liquid. Examples of this include

a pharyngeal squeeze manouevre,[47] forced breath hold to assess maintenance of volitional glottic closure and a dry swallow. A range of fluid and food can be given, without requiring the addition of radio-opaque contrast. Food colouring is added to enhance visibility. For patients with severe dysphagia, the swallow trial may just consist of an ice chip as described by Langmore.[42]

Similar to VFSS, compensatory strategies may be introduced and their effectiveness evaluated. Images are recorded digitally, for later analysis and interpretation. Specific patient safety procedures need to be in place, such as guidelines for epistaxis or laryngospasm. Local guidelines on sterilization and infection control need to be followed.

CONTRAINDICATIONS AND RISKS

FEES has a good safety record, but it may be unsuitable for those patients who are drowsy or are unable to cooperate. Caution is needed in patients with a history of bronchospasm or laryngospasm, vasovagal response, cardiac instability, severe epistaxis or a physical obstruction to the passing of the scope. Adverse reactions to the topical anaesthetic are rare, but clinicians should take an adequate case history, adhere to recommended doses and have resuscitation measures available.

ANALYSIS

Interpretation of a FEES includes a description of bolus flow, reactions to a misdirected bolus, presence of airway invasion, residue and variations from the normal anatomy and physiology. Specific measurements relating to initiation of the swallow (also referred to as 'dwell time') may be taken.[48] The presence of post-swallow residue and airway invasion are recorded.

LIMITATIONS

There are a number of limitations of FEES, including:

- There is no view for evaluation of the oral stage of swallowing.
- There is loss of view ('whiteout') during the swallow due to pharyngeal constriction around the endoscope lens.
- Quantitative measures of structure displacement (e.g. hyoid elevation) are not possible.
- Ability to estimate amount of aspirated material is limited.

VFSS and FEES are widely used as instrumental assessments of oropharyngeal dysphagia in routine clinical practice. They are complimentary functional investigations.[49, 50] The features of each examination are summarized in **Table 50.1**.

Transnasal oesophagoscopy

Transnasal oesophagoscopy (TNO) is now a widely available technique for visualization of the upper digestive tract without the need for sedative drugs. This is discussed in greater detail in Chapter 49, Causes and assessment of dysphagia and aspiration. The role of TNO in functional investigations of the upper digestive tract is mainly in the exclusion of structural pathology, such as strictures or malignancies, and also in the diagnosis of other pathology, such as oesophagitis, through visual assessment and biopsy.[51]

MANOMETRY

Manometry provides additional swallowing information and evaluates pressure changes from pharyngeal and oesophageal muscle activity, particularly in patients with motility disorders.[52]

TABLE 50.1 Comparison of VFSS and FEES

Considerations	FEES	VFSS
Equipment	Nasoendoscope, camera, monitor, digital recorder, microphone	Fluoroscopy, digital recorder, monitor
Personnel	Otolaryngologist and/or SLT	Radiologist and/or radiographer, SLT
Safety	Mild patient discomfort	Radiation exposure
Accessibility	Highly portable, repeatable	X-ray department only; repeated assessment limited by radiation
Oral stage	Not observed	Well seen
Pharyngeal stage	Direct assessment before and after swallowing, not during	Well seen
Oesophageal stage	Not observed	Can be observed
Aspiration/penetration	Accurate assessment	Accurate assessment
Pharyngeal sensation	Sensory response to the scope can be observed	Only inferred
Range of boluses	All ranges of food and drink	Radio-opaque contrasts alter viscosity, texture and taste of food/drink
Fatigue effect on swallow	Easily assessed	Limited by radiation and expense

Pharyngeal manometry

Pharyngeal manometry provides information regarding the amplitude and duration of pharyngeal contractions and upper oesophageal sphincter (UOS) relaxation during swallowing. Rates of pressure change are greater in the pharynx than the oesophagus. Clinically, this test gives an indication of the strength and consequently the efficiency of essential swallowing movements. This can assist in understanding the nature of the swallow breakdown, particularly with motility disorders and post-swallow pharyngeal residue. Manometry can be used in conjunction with the tools mentioned above, i.e. videofluoroscopy (manofluoroscopy) or endoscopy (manovideoendoscopy). It may be used as a stand-alone measure, when the swallowing physiology has already been studied and is known. However, when used alone, it will be susceptible to technical difficulties with accurate sensor placement and reduced inter- and intrareliability.

Three main measures of timing and pressure generation are derived from the procedure:

- base of tongue to pharyngeal wall pressure generation
- lower pharyngeal pressure
- UOS relaxation.

A healthy swallow is characterized by rapid onset of pharyngeal pressure generation, a drop in UOS pressure in response to laryngeal elevation and a return to baseline pressure measurement post swallow.

PROCEDURE

Pharyngeal manometry is moderately invasive, requiring placement of a specialized catheter through the nose and into the oesophagus. This needs to remain in the correct position during swallowing, which can be problematic due to the upward movement of the larynx. The distal tip needs to remain in the UOS, for the assessment of cricopharyngeal relaxation. The proximal end of the catheter is secured with tape against the face. Microcatheters are required if this test is to be performed in children. Patients may require a little time to accommodate to the catheter *in situ*. Measurements are taken at rest and during swallowing.[52]

Research reporting normative data is available. Readings can differ according to age, gender, viscosity and bolus volume[53, 54] so a standardized approach is necessary for comparisons. There is less variation in resting UOS pressures.[53] Measurements appear consistent across swallows, limiting the need for repeated trials.[55, 56] Training is required for interpreting results, with just short training affording high levels of reliability.[57] The measures derived are useful outcome measures for guiding and evaluating treatment.

Oesophageal manometry

Oesophageal manometry provides information on oesophageal muscle activity and can be useful in diagnosing oesophageal motility disorders. The oesophageal peristaltic wave pressure rises slowly to approximately 50 mmHg, and falls rapidly. Secondary peristaltic waves arise locally in response to distension, needed for more solid bolus transportation. Tertiary oesophageal contractions are irregular, non-propulsive contractions involving long segments of the oesophagus.[37]

The 3 cm long lower oesophageal sphincter (LOS) behaves like the UOS, but with a lower tonic (resting) contraction pressure of 10–30 mmHg relative to intragastric pressure. It remains closed except for relaxation when the bolus and peristaltic wave arrive, as swallowing induces inhibition of LOS tone activity. The barrier formed by LOS tonic pressure is lower after meals and tighter at night. Similar to the UOS, measurement of the LOS tonic pressure is complicated by radial asymmetry and a respiratory pressure fluctuation.

HIGH-RESOLUTION MANOMETRY (HRM)

Conventional pharyngeal or oesophageal manometry utilizes a solid-state catheter with sensors spaced at intervals along the catheter. Sensors are unidirectional and record pressure changes shown as pressure waveforms. The enhanced technology of HRM offers several advantages over conventional manometry. The catheter has 36 circumferential pressure sensors, at 1 cm apart, thus providing greater specificity and accuracy. Output is interpreted from a spatiotemporal plot, requiring manual analysis.

PATIENT SELECTION

Manometry is not frequently used as part of a routine clinical assessment in the UK. Robust guidance on who to select for this procedure is still in its infancy. However, the information derived can help to form a more detailed understanding of swallow breakdown. A small number of patients may not be able to tolerate the passage of a nasopharyngeal catheter and this may be contraindicated in those with recent nasopharyngeal surgery. Patients with suspected Zenker's diverticulum will require X-ray guidance, to ensure correct catheter placement into the upper oesophagus. The range of manometric findings for different pathological processes is dealt with in Chapter 49, Causes and assessment of dysphagia and aspiration, and Chapter 53, Oesophageal diseases.

OTHER INVESTIGATIONS

Respiration

Respiratory recordings measure the duration and timing of deglutition apnoea, and direction and rate of airflow and thus a more complete picture of the physiology of swallowing.[58, 59] Several assessment tools have been used and reported in the literature, including intranasal pressure measurements, resistive chest belt, nasal thermistor and respiratory inductive plethysmography.[60–63] Continuous recordings of oxygen saturation by pulse oximetry have also been investigated as a possible marker of aspiration, with conflicting results.[64–67]

Ultrasound

Ultrasonography is a non-invasive technique for soft-tissue imaging during swallow events. The ultrasound transducer with high-frequency sounds (>2 MHz) is placed submentally to produce dynamic images of the soft tissue in the oral cavity and parts of the oropharynx, hyoid motion and changes to hyoid–thyroid distance. The quality of the tongue image for measuring movements is not easy to interpret.[37, 68] It cannot visualize episodes of penetration or aspiration. Patients need to maintain sufficient head control during this examination. There are further methodological issues such as accuracy of transducer placement and reliability of measurements.[69]

Pharyngeal and oesophageal pH monitoring

Prolonged (24-hour ambulatory) pH monitoring is the most reliable method of diagnosing gastro-oesophageal reflux disease (GORD). Recently, the introduction of pharyngeal probes has resulted in the technique being used to diagnose laryngopharyngeal reflux (LPR). Technological advances have led to the, single, dual and even triple lumen sensors that can detect liquid reflux events as well as purported aerosolized acid exposure at various points along the upper digestive tract.[70, 71]

In oesophageal pH monitoring the distal oesophageal pH probe is placed 5 cm above the LOS (position determined by manometry) and the proximal one below the UOS, thus any reflux is measured along the entire length of the oesophagus. The pharyngeal probe is typically placed at the level of the uvula; there is, however, inconsistency in the methodology of pH monitoring in much of the published literature, in particular location of the pharyngeal probe.[72] Further limitations identified in pH monitoring include the impact of diet[73] and the role of non-acidic factors, particularly in LPR.[74] A recent meta-analysis of pH manometry showed that, when techniques were tightly controlled, consistent differentiation of LPR patients from healthy controls was possible.[72] Nevertheless, oesophageal and pharyngeal pH manometry does require specific invasive equipment. This invasive technique prevents some patients from undertaking activities that provoke reflux during the investigation, so it can lead to underestimating their problems.[75]

Scintigraphy

This procedure tracks movement of the bolus over time and quantifies the residual bolus in the oropharynx, larynx and trachea, using radionuclide material with liquid or food, and a gamma camera. It can offer information regarding oesophageal transit.[76] Although it can detect aspiration and reflux, it has poor anatomical definition in comparison to VFSS or barium swallow, and it does not image the biomechanics of swallowing, thus the cause of aspiration cannot be determined.

Lingual pressure recording

Tongue strength and endurance are important components for bolus pressure drive. Three-bulb linear manometric sensor arrays have been used to evaluate the timing and pressure patterns of the anterior, middle and posterior tongue during the oral phase of swallowing. Small pressure sensors are attached to the palate. Most work to date has been experimental.[77]

Electromyography

Surface electromyography (sEMG) measures the amplitude of submental muscle activity from electrodes placed under the chin, in combination with a laryngeal sensor. Activity is recorded from any or all of the submental muscles during swallowing. They are variable in their order of activation both within and between subjects. Preliminary evidence suggests that it may be an important adjunct in identifying aspiration risk in acute stroke patients.[78]

CONCLUSION

Manometry, nasendoscopy and videofluoroscopy are complementary procedures which enhance our understanding of the pathophysiological processes causing symptoms and inform management decisions. Other techniques mentioned are either at experimental stages requiring more research-based data, or are for specific conditions related to dysphagia.

BEST CLINICAL PRACTICE

- ✓ After careful history-taking, evaluation of symptomatology and a clinical swallow evaluation, choosing the most appropriate investigation for any one patient depends on many factors:
  - ✓ specific symptoms of dysphagia
  - ✓ medical condition, cognitive functioning, fatigue level and mobility of patient
  - ✓ invasive nature of investigations and the likely effect(s) this may have
  - ✓ availability and cost of both equipment and trained/experienced professionals.
- ✓ Each investigation has different advantages and limitations, as listed in detail in the chapter.
- ✓ Some patients may require several investigations for a more complete picture but, in general, FEES and/or videofluoroscopy are the first choices for oropharyngeal dysphagia, followed by manometry for motility disorders and to identify candidates for myotomy or dilatation. Barium contrast identifies anatomical and some motor disorders; endoscopy of the oesophagus is the approach of choice for obstructions, taking biopsies for pathologic identification, therapeutic dilatation of a stricture or removal of foreign bodies.
- ✓ The two techniques of videofluoroscopy and FEES are equally effective in discrimination between penetration and aspiration and in guiding management with respect to the outcome of pneumonia.

KEY POINTS

- Functional investigations of the upper GI tract to explore oropharyngeal dysphagia provide information about anatomy, muscular function, mucosal sensation, bolus direction and flow, and the relationships between them. This information is important for devising management recommendations, shared decision-making and evaluating treatment over time.
- Oropharyngeal dysphagia is caused by many underlying aetiologies, producing a wide range of symptoms. The selection of functional assessments will depend on the clinical question needing to be answered.
- Non-instrumental and screening tests are useful to detect the presence of dysphagia. However, functional investigations using instrumentation are more sensitive and specific in accurately detecting aspiration or penetration.
- Instrumental tests, such as videofluoroscopy and FEES, are diagnostic assessments as they can define the swallow disorder in terms of anatomy and physiology causing the problem, and the symptoms in terms of aspiration, penetration, reflux and residue. Such information enables treatment to be directed at the physiological disorder(s) while symptoms are managed by compensatory strategies.
- Technological advancements are allowing for a multitude of further advanced assessments of the upper GI tract and are useful for specific clinical scenarios.

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CHAPTER 51

PHARYNGITIS

Sharan Jayaram and Conor Marnane

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SEARCH STRATEGY

Data in this chapter may be updated by a Medline search using the keywords: acute pharyngitis, sore throat, acute tonsillitis, streptococcal pharyngitis/sore throat, bacterial pharyngitis/sore throat, viral pharyngitis/sore throat; peritonsillar abscess alone and with epidemiology, bacteriology, clinical features, differential diagnosis, investigation, treatment and complications; infectious mononucleosis, glandular fever and Epstein–Barr virus, both in isolation and in conjunction with, epidemiology, clinical features, systemic manifestations, associated tumours, serological diagnosis and treatment; chronic pharyngitis/ nonspecific chronic pharyngitis or non-infectious chronic pharyngitis.

In addition, the Cochrane Database of Systematic Reviews and the references in the Scottish Intercollegiate Guidelines Network (SIGN) were reviewed.

DEFINITION

Pharyngitis is defined as inflammation of the pharynx. It can be generalized inflammation of the whole pharynx (**Figure 51.1**) or localized to a specific area of the pharynx (tonsillitis, **Figure 51.2**). The presenting symptom of pharyngitis is usually a sore throat, which is one of the most common presentations for outpatient consultations in primary care.

EPIDEMIOLOGY

Pharyngitis affects both sexes and all age groups, but it is more common in children in late autumn and early winter. The overall incidence of sore throat in all age groups varies widely and different definitions make comparisons between figures difficult. Moreover, most patients with sore throat never or only rarely see their GP. A study demonstrated that only 1 in 18 sore throat episodes led to a GP consultation.[1]

In 2007, the age-standardized patient prevalence rate for acute pharyngitis for all ages in UK was 182 per 10 000.[2]

The cost to the UK National Health Service (NHS) of GP consultations for sore throat, before any treatment or investigation, has been estimated at approximately £60 million per annum.

AETIOLOGY

Most cases of pharyngitis are due to infectious causes (**Box 51.1**). Viruses are isolated in approximately 40–60% of cases and bacterial pathogens in approximately 5–30% of cases. In approximately 30% of cases no pathogen is isolated.

Non-infectious causes include dry air, allergy/post-nasal drip, chemical injury, gastro-oesophageal reflux disease (GORD), smoking, neoplasia and endotracheal intubation.

GABHS BACTERIAL PHARYNGITIS

Group A beta-haemolytic streptococci (GABHS) are the commonest cause of bacterial pharyngitis and are spread via respiratory secretions through close contact. There is

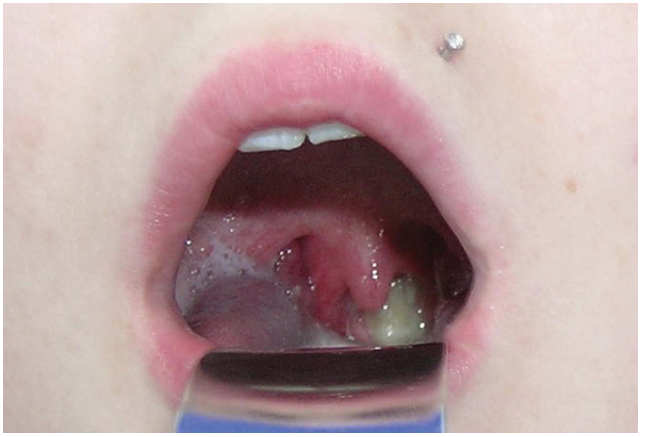

Figure 51.1 Acute pharyngitis with a mucopurulent secretion on the posterior pharyngeal wall.

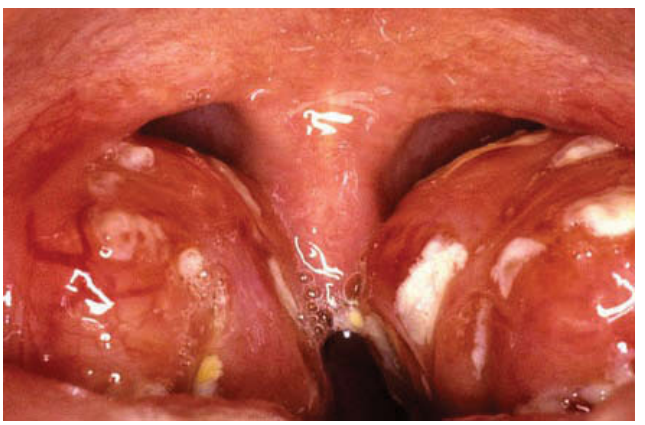

Figure 51.2 Clinical appearance of tonsillitis with pharyngeal erythema, enlarged tonsils and tonsillar crypts containing necrotic or purulent exudates.

an incubation period of 1–5 days. The risk of contagion most probably depends on inoculum size and the virulence of the infecting strain. Individuals are most infectious in the early stages of the disease. More than 120 M-protein types of GABHS have been isolated, with serotypes 1, 3, 5, 6, 18, 19 and 24 associated with rheumatic fever (i.e. rheumatogenic forms) and others, such as serotypes 49, 55 and 57 associated with pyoderma and acute post-streptococcal glomerulonephritis.

Clinical presentation

The classical history is that of sore throat, fever, chills, malaise, headaches, anorexia, abdominal pains as well as a history of exposure to known carriers. However, all these features are rarely present, but sore throat is present in all those old enough to recognize the symptom (see **Figure 51.1**).

The clinical picture in an individual sore throat is of limited assistance in distinguishing between a bacterial and a viral aetiology. There is no evidence that bacterial sore throats are more severe than viral ones or that the duration of the illness is significantly different in the two types.

BOX 51.1 Causes of pharyngitis

Bacterial	
Common	Group A-beta haemolytic *Streptococcus pyogenes (GABHS)*
Uncommon	*Neisseria gonorrhoeae* *Haemophilus influenza* *Corynebacterium diphtheria* *Moraxella (Branhamella) catarrhalis* Group C and G streptococci *Corynebacterium haemolyticum* *Chlamydia trachomatis* *Mycoplasma pneumonia* *Borrelia* species *Francisella tularensis* *Yersinia* species
Probable co-pathogens	*Staphylococcus aureus* *H. influenza* *Branhamella catarrhalis* *Bacteroides fragilis* *Bacteroides oralis* *Bacteroides melaninogenicus* *Fusobacterium* species *Peptostreptococcus* species
Viral	
	Rhinovirus *Adenovirus* *Parainfluenza* virus Coxsackievirus *Coronavirus echovirus* Herpes simplex virus Epstein–Barr virus (EBV) (mononucleosis) Cytomegalovirus (CMV) Human immunodeficiency virus (HIV) infection
Fungal	*Candida* species
Protozoa	*Toxoplasma gondii*
Non-infectious causes	Dry air Allergy/post-nasal drip Chemical injury Gastro-oesophageal reflux disease (GORD) Smoking Endotracheal intubation

Although no single or combination of physical findings is specific for distinguishing GABHS from viral aetiologies, several features are suggestive (**Box 51.2**).[3]

Specific viral infections have characteristic features: conjunctivitis more commonly with adenovirus infections, infectious mononucleosis (IM) typically is exudative and associated with extensive false membranes; finally, herpangina (usually coxsackievirus A or herpes virus) is associated with papulovesicular lesions. Concomitant vesicles on the hands and feet are associated with coxsackievirus A (hand, foot and mouth disease).

Several scoring systems have been described to provide a rational basis for differentiating GABHS from viral pharyngitis. SIGN guidelines[4] recommend that the Centor clinical prediction score should be used to assist the decision on whether to prescribe an antibiotic but cannot be relied upon for a precise diagnosis.

BOX 51.2 Features distinguishing GABHS pharyngitis from viral pharyngitis

Features suggestive of bacterial pharyngitis	Features suggestive of viral origin
Pharyngeal erythema Enlarged tonsils Tonsillar crypts containing necrotic or purulent exudates Fever Cervical lymphadenopathy Soft palate petechiae Scarlet fever rash (punctate erythematous macules with reddened flexor creases and circumoral pallor), also called 'sandpaper' rash History of exposure 5–15 years age group	Conjunctivitis Sneezing and rhinorrhea Cough Diarrhoea Exanthems or enanthems Papulovesicular lesions

The Centor score[5] gives 1 point each for:

- tonsillar exudate
- tender anterior cervical lymph nodes
- history of fever
- absence of cough.

McIsaac et al[6] developed the modified Centor criteria, which add the age of the patient (+1 if age 3–14, 0 if age 15–44 and –1 if age ≥45), taking into account the fact that GABHS is more prevalent in the age group of 5–15 years.

The likelihood of GABHS infection increases with increasing score, and it is 25–86% with a score of 4 and 2–23% with a score of 1, depending upon age, local prevalence and seasonal variation.[4] The score is not validated for use in children under 3 years.

Studies on sensitivity and specificity suggest that reliance on clinical diagnosis will miss 25–50% of GABHS pharyngitis cases and that 20–40% of those with negative throat cultures will be labelled as having GABHS.

Investigation

Investigations are of limited practical value but may occasionally be of benefit when symptoms are severe or if they persist despite adequate conservative management. Full blood count may show leukocytosis, which is highly suggestive of bacterial infection.

Recommendation regarding routine use of tests for microbiological diagnosis of GABHS varies among national guidelines.

According to US[7,8] and French[9] guidelines, microbiological confirmation is required for the diagnosis of GABHS pharyngitis, and rapid antigen detection tests (RADTs) or throat culture should be routinely performed in suspected cases. However, according to UK guidelines, further studies are required to evaluate the cost-effectiveness and clinical benefit of RADTs and insufficient evidence was identified to support a recommendation (SIGN).

RADTs involve extraction of the group-specific carbohydrate antigen from the GABHS cell wall and identification of the antigen by an immunological reaction. A recent meta-analysis of these tests[10] determined an overall sensitivity of 0.85 [95% CI, 0.84–0.87], specificity was 0.96 [95% CI, 0.96–0.97], likelihood ratio (+) 22.21 [95% CI, 15.12–32.63], and likelihood ratio (–) 0.15 [95% CI, 0.13–0.18].

A well-conducted prospective study showed that the RADT can be a valid diagnostic test for the diagnosis of GABHS in adults with pharyngitis, particularly when combined with the Centor clinical score and should be used in patients with at least two clinical findings suggestive of GABHS.[11]

It has been suggested that a strategy based on clinical scores alone may be associated with higher antibiotic usage as compared with either (i) a combination of clinical score and rapid tests use or (ii) use of rapid tests alone.[12] Rapid antigen detection, however, is not sensitive for group C and G streptococci or other bacterial pathogens.

Throat culture is described as the criterion (gold-standard) diagnostic test for GABHS in the North American literature. Results can take up to 24 hours. Throat culture results are highly sensitive and specific for GABHS but can vary, depending on technique, sampling and media. A positive throat culture for GABHS makes the diagnosis of streptococcal sore throat likely but a negative culture does not rule out such a diagnosis. There are cases where *Streptococcus* is isolated from sore throats but there is no serological evidence of infection.[13] There is also a high asymptomatic carrier rate of up to 40% for GABHS.[14] The flora of bacteria recovered from the surface of the tonsil correlates poorly with that deep in the tonsillar crypts, which is the most likely cause of infection.[15,16] Symptoms also correlate poorly with results of throat swab culture.[17] Throat swabs are neither sensitive nor specific for serologically confirmed infection, increase costs considerably, may medicalize illness and alter few management decisions. **Throat swabs should not routinely be carried out in sore throat.**[18]

Antistreptococcal antibody titres reflect past and not present immunologic events and therefore cannot be used to determine whether an individual with pharyngitis and Group A streptococcus (GAS) in the pharynx is truly infected or merely a streptococcal carrier.

Treatment

Streptococcal pharyngitis usually has a 5–7-day self-limiting course. Non-steroidal anti-inflammatory drugs (NSAIDs) and paracetamol are more effective than placebo for relief of symptoms.[19] Paracetamol will suffice for mild cases, but in adults NSAIDs such as ibuprofen and diclofenac are considered superior to paracetamol for pain relief.[12]

Although concerns about risks of NSAIDs have been raised, a large double-blinded randomized controlled trial (RCT) showed that ibuprofen is as well tolerated as paracetamol,[20] hence the SIGN guidelines recommend use of ibuprofen 400 mg thrice daily for symptomatic relief of sore throat, fever and headache, in accordance with the

usual contraindications. Ibuprofen should not be given to patients with or at risk of dehydration due to concerns regarding renal toxicity. In patients who have contraindications for ibuprofen, paracetamol 1 g q.i.d. is recommended. However, in children paracetamol should be used as the first choice, with ibuprofen being used as an alternative.

TOPICAL ANALGESIA

A recent placebo-controlled study suggested that chlorhexidine gluconate and benzydamine hydrochloride mouth spray, added to standard antibiotic treatment, significantly alleviate the intensity of clinical signs in patients with streptococcal pharyngitis.[21]

Based on *in vitro* studies, amylmetacresol and 2,4-dichlorobenzyl alcohol (AMC/DCBA)-containing throat lozenges have been thought to produce an analgesic effect by means of its antiseptic action on bacteria and viruses and partly due to sodium channel blocking, i.e. direct local anaesthetic-like effects.[2] However, in the absence of good quality evidence confirming their efficacy or lasting benefit, there is insufficient evidence to support a recommendation of use of topical analgesia.

CORTICOSTEROIDS

According to a recent Cochrane review, in adult patients with sore throat, pain can be reduced and resolution hastened by use of a single dose of oral or intramuscular corticosteroids in conjunction with antibiotic therapy.[22] Two studies which directly compared intramuscular and oral routes found no differences and it is suggested that the oral route is used. Patients taking corticosteroids were three times more likely to experience complete resolution of their sore throat symptoms by 24 hours compared to those taking placebo. The mean time to onset of pain relief was 6.3 hours earlier in participants taking corticosteroids compared to placebo. However, these modest benefits have to be balanced with possible adverse drug effects of steroids,[23] although it is suggested that a short course is unlikely to be harmful.

There was insufficient evidence to recommend steroids in children with sore throat or as stand-alone treatment without the use of concurrent antibiotics.

ANTIBIOTICS

Bacterial pathogens are responsible for only 5–30% of cases of acute pharyngitis.[24] It is therefore illogical to treat all sore throats with antibiotics, and there is a favourable outcome in the majority of cases even when antibiotics are withheld. An open study of prescribing strategy in over 700 patients randomized to antibiotic versus no prescription versus delayed prescription for 3 days showed no difference in the main outcomes.[25]

A recent assessment of Cochrane reviews suggests that, for streptococcal tonsillitis, the use of antibiotics seems to be discretionary rather than prohibited or mandatory. This is because the benefit in terms of symptoms is only about 16 hours compared with placebo.[26] Estimates of the number of people with sore throat who must be treated to resolve the symptoms of one of them by day 3 (i.e. the number needed to treat to benefit (NNTB)) varied between 3.7 and 14.4, with benefit being more pronounced in patients with a positive throat swab for *Streptococcus*.

Role of antibiotics in preventing complications

Although the Cochrane review on the role of antibiotics found that antibiotics reduced the rate of non-suppurative complications such as rheumatic fever to about one-quarter of that in the placebo group and the rate of suppurative complications to about one-third, most of the beneficial effects were seen in studies conducted before 1975. The incidence of rheumatic fever in the UK is extremely low and there is no support in the literature for the routine treatment of sore throat with penicillin to prevent the development of rheumatic fever.[17] Protecting sore throat sufferers against suppurative and non-suppurative complications in high-income countries requires treating many with antibiotics for one sufferer to benefit. This NNTB may be lower in low-income countries as acute rheumatic fever remains a major problem in tropical regions, resource-poor countries and minority indigenous communities, with Aborigines in central and northern Australia showing some of the highest rates of both acute rheumatic fever and rheumatic heart disease in the world. Study of this latter group suggests that group C and G streptococcal organisms as well as the usual group A streptococcal infections may also have rheumatogenic strains.[18] Similar considerations apply to the prevention of glomerulonephritis.[19]

Recommendation regarding role of antibiotics

Most guidelines[4, 12, 27] recommend that antibiotics should not be prescribed for symptomatic management of pharyngitis, especially in patients with less severe presentation (e.g. 0–2 Centor criteria). Antibiotics should be considered in patients with more severe presentations (when three or more Centor criteria are present), but the modest benefit in symptoms from antibiotics should be weighed against increased antibacterial resistance, costs and possible side effects.

Antibiotics need not be started immediately. A Cochrane review evaluated the use of delayed antibiotics (more than 48 hours after presentation) compared to immediate or no antibiotics as a prescribing strategy for acute upper respiratory tract (URT) infections.[28] No significant differences in outcome were observed among the three groups, which led the authors to conclude that, in patients with respiratory infections where clinicians feel it is safe not to prescribe antibiotics immediately, no antibiotics with advice to return if symptoms do not resolve is likely to result in the least antibiotic use, while maintaining similar patient satisfaction and clinical outcomes to delayed antibiotics.

Patient and doctor education on the lack of benefit of antibiotics in routine management of sore throat can have a significant impact on the amount of antibiotics prescribed.[29]

Choice of antibiotics

Penicillin has been the antimicrobial agent of choice for GABHS and is recommended by most guidelines, if an antibiotic is deemed necessary for the management of pharyngitis. The minimal inhibitory concentration of penicillin for GABHS has not shown an increase over at least five decades.[30]

Most trials have compared penicillin with a variety of other antibiotics, notably cephalosporins. Although optimum elimination of GABHS is secured with intramuscular long-acting penicillin, oral penicillin V, 500 mg, four times daily for 10 days (adults) is the recommended dosage[4] and is widely regarded as the gold-standard treatment, with the advantages of being cost-effective and well-tolerated. A 10-day course of penicillin appears to be more effective than a 5-day course in reducing the incidence of bacteriological treatment failure, characterized by the presence of the same seroptype of GABHS in follow-up throat cultures.

Other more expensive antibiotics, mainly cephalosporins, have been shown to be statistically significantly more successful in eradicating the organism although the clinical advantage is much less clear. Some cephalosporins offer a more convenient dosage regimen, but twice and three times daily dosage of oral penicillin V has also been shown to be effective in eliminating GABHS. A 2010 Cochrane review[31] noted that, although there seem to be indications that carbacephems and cephalosporins might have some benefit over penicillin in terms of resolution of symptoms and incidence of relapse, the findings were inconsistent across analysis methods and the NNTBs were substantial. Therefore there is insufficient convincing evidence to alter current guideline recommendations for the treatment of patients with GABHS tonsillopharyngitis.

In patients allergic to penicillin, the alternatives include narrow-spectrum cephalosporins (cephalexin, cefadroxil) or macrolides (azithromycin, clarithromycin).

Doctors need to be aware that IM may present with severe sore throat with exudate and anterior cervical lymphadenopathy, and therefore should avoid prescription of ampicillin-based antibiotics, including co-amoxiclav, as first-line treatment.

When sore throat recurs in patients who have received antibiotic treatment, the reasons may include inappropriate antibiotic therapy, inadequate dose or duration of previous therapy, patient non-compliance/non-concordance, reinfection and local breakdown of penicillin by beta-lactamase producing commensals. Benzathine penicillin, cefuroxime and clindamycin have been shown to be superior to penicillin V in the management of children with this problem, and they may reduce the frequency of episodes.

ROLE OF TONSILLECTOMY IN THE MANAGEMENT OF PHARYNGITIS/TONSILLITIS

Although the non-inflammatory indications for tonsillectomy are reasonably defined with further trials in progress, the indication for tonsillectomy in the setting of recurrent/chronic tonsillitis/pharyngitis is controversial, with varied opinions regarding the relative risks and benefits. The controversy stems from the fact that palatine tonsils are only one constituent of the Waldeyer's ring of lymphoid tissue within the pharynx. Therefore, a patient who has had the tonsils removed can still have inflammation of the surrounding lymphoid tissue leading to recurrent sore throat. Hence, the important clinical question is to differentiate patients with recurrent tonsillitis from those with recurrent generalized pharyngitis presenting with sore throat. The natural history of tonsillitis is for the episodes to become less frequent with time, but there are insufficient epidemiological data for all age groups to allow predictions of this to be made in individual patients.

Various criteria have been proposed to select patients who are most likely to benefit from tonsillectomy. The referral criteria for tonsillectomy in the presence of recurrent sore throat that are used currently in the UK are based on the SIGN guidelines,[4] which are adapted from Paradise et al:[32]

- Sore throats are due to acute tonsillitis
- The episodes of sore throat are disabling and prevent normal functioning
- Seven or more well-documented, clinically significant, adequately treated sore throats in the preceding year *or*
- five or more such episodes in each of the preceding 2 years *or*
- three or more such episodes in each of the preceding 3 years.

Cognisance should also be taken of whether the frequency of episodes is increasing or decreasing.

A 2009 Cochrane review looked at the benefits of tonsillectomy compared with non-surgical treatment in the management of chronic or recurrent acute tonsillitis.[33] In this review, Burton et al observed that good information about the effects of tonsillectomy was only available for children and for effects in the first year following surgery. Children were divided into two subgroups: those who are severely affected (based on specific criteria which are often referred to as the 'Paradise criteria') and those less severely affected. Severely affected children will on average have one rather than three unpredictable episodes of any type of sore throat in the first year post-surgery, at the cost of one additional episode of post-operative pain. In the less severely affected group, surgery will mean having an average of two rather than three unpredictable episodes of any type of sore throat. Although the size of the effect is modest, the authors concluded there may be a benefit to knowing the precise timing of one episode of pain lasting several days; it occurs immediately after surgery as a direct consequence of it.

Several non-controlled studies suggest that tonsillectomy in children leads to an improvement in their general health and well-being.[34, 35]

The Cochrane review cited above found limited evidence of benefit of tonsillectomy in adults. One small well-conducted RCT[36] which looked at the effects of tonsillectomy in adults with proven recurrent group A streptococcal pharyngitis over a very short period

demonstrated a modest benefit; one episode of post-operative pain led to 1.5 fewer episodes of sore throat in the first 6 months.

These benefits have to be assessed keeping in mind that tonsillectomy is associated with a small but significant degree of morbidity in the form of primary and secondary haemorrhage. Patients who choose surgery for themselves or parents who choose it for their child must therefore be fully informed of the benefits and risks of the procedure.

THE CARRIER STATE

Patients exposed to GABHS may continue to carry the organism asymptomatically even after adequate antibiotic therapy. Carriers are recognized as those who demonstrate a positive culture but no rise in antistreptolysin O convalescent titre, and rates reported in the literature vary between 3% and 40% depending on the population studied. Carriers are at little risk of transmitting the disease: only 3.5% produce disease within their families.

Complications

Complications of GABHS pharyngitis can be classified as suppurative and non-suppurative (**Box 51.3**).

SUPPURATIVE COMPLICATIONS

Peritonsillar abscess (quinsy)

Peritonsillar abscess (PTA) is a collection of pus between the fibrous capsule of the tonsil, usually at the upper pole, and the superior constrictor muscles of the pharynx.

Epidemiology

Data from England have suggested that there was an 18% increase in the incidence of PTA in the 10 years to 2012, with 7589 episodes seen in 2009–2010.[37] It has been hypothesized that it could be because of fewer tonsillectomy operations being performed during that same period.

It may happen at any age but the majority of abscesses are seen in young adults between 20 and 39 years of age, which is surprising in view of the fact that the incidence of tonsillitis peaks in childhood, suggesting the aetiology must be more complex.

Several factors are known to increase the predisposition to form PTA. They include age, male gender, smoking, poor dental hygiene and immunodeficiency.

Pathogenesis

Two mechanisms have been proposed to describe the pathogenesis of PTA:[38]

- **A complication of acute tonsillitis.** This has been the most accepted theory, but recently questions have been raised about this hypothesis. This is because of certain studies which demonstrated up to 68% of patients with PTA had no preceding history of tonsillitis.[39, 40] The other factor which goes against this theory is the fact that the incidence of PTA is highest in the 20–39 age group whereas acute tonsillitis has the highest incidence in the 5–15 age group.
- **Weber gland blockage.** Passy[41] introduced the theory that a PTA may also represent a sequela of damage to Weber's glands, which are minor salivary glands located in the supratonsillar space. It has been suggested that the production of saliva by these glands helps to keep the tonsillar crypyts and peritonsillar areas clean. Poor dental hygiene and localized Weber gland infection could lead to blockage of the gland or the draining duct, predisposing this area to abscess formation.[41, 42] The reduction of innate immunity provided by saliva could be a contributing factor.[43]

Bacteriology

Group A beta-haemolytic streptococci and anaerobes such as *Fusobacterium necrophorum* and *Streptococcus milleri* have been clearly identified as causative organisms in PTA.[38]

Powell et al[38] suggested that there seem to be predominantly two pathogenically different PTA subtypes. Type 1 contains a pure culture of a single organism, most often GABHS. Type 2 displays heavy polymicrobial growth, often containing a variety of facultative and obligate anaerobes. Clinically, type 2 PTA often appears to be more severe, probably due to synergistic microbial interactions.

Clinical features

The main feature of the history is the progressive, usually unilateral, sore throat over 3–4 days, odynophagia, dysphagia for solids and eventually liquids, drooling of saliva, trismus, ipsilateral otalgia and headache associated with fever, lethargy and ipsilateral lymphadenopathy. The patient often develops a 'plummy' voice secondary to the oropharyngeal swelling and, on examination, limited mouth opening is virtually pathognomonic.[44] The tonsil is displaced medially by the hyperaemic, bulging mucosa of the anterior pillar over the peritonsillar space (**Figure 51.3**) and, in addition, the jugulodigastric nodes are tender and enlarged. Bilateral quinsies have been reported[45, 46] and in association with IM.[47] PTA arising in patients with IM is not linked to steroids prescribed to relieve upper airways obstruction in these circumstances.[48]

BOX 51.3 Complications of GABHS pharyngitis

Suppurative	Non-suppurative
Peritonsillar abscess Parapharyngeal abscess Retropharyngeal abscess	Rheumatic fever Post-streptococcal reactive arthritis Post-streptococcal glomerulonephritis Scarlet fever Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS)

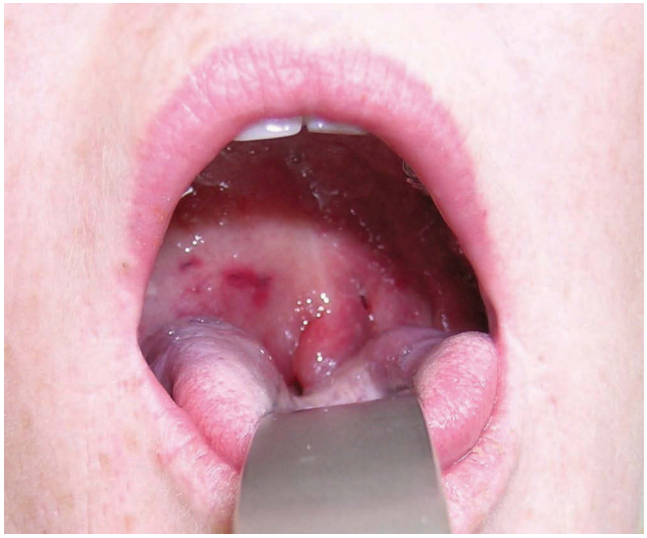

Figure 51.3 Peritonsillar abscess showing tonsils displaced medially and a bulge of the anterior tonsillar pillar.

Investigation

Investigation is not mandatory in clear-cut cases but may be helpful in less straightforward cases.

Needle aspiration of pus is often curative and may also provide useful bacteriology in recurrent or non-responsive quinsies and help clarify the difference between peritonsillar cellulitis and PTA. Bacteriological specimens do not need to be sent to the laboratory routinely after needle aspiration; this should be reserved for patients with a high likelihood of infection by resistant organisms, such as diabetics, immunocompromised patients or patients with recurrent PTAs.[49]

Although traditionally routine screening for IM in all patients presenting with PTA had been recommended,[50] a recent evidence-based review suggests that tests for infective mononucleosis should be reserved for cases were clinical suspicion is high, such as in teenagers and young adults and those with general features that are suggestive of infective mononucleosis.[37]

Transoral ultrasound is used in some countries[51] as an effective non-invasive method of differentiating pus from cellulitis (sensitivity 92.3%, specificity 62.3%).

Dental radiographs or an orthopantomogram may be helpful in the presence of coincidental dental disease or uncertainty as to whether a dental abscess may be involved.

Computed tomography (CT) has been used in the presence of suspected complications such as spread to the parapharynx, retropharynx and mediastinum. If descending necrotizing mediastinitis is suspected, CT of the neck and chest is the investigation of choice, rather than chest radiograph, as it will pick up signs when the chest radiograph is still normal.[52]

Magnetic resonance imaging (MRI) allows better soft-tissue detail and MR angiography may be suitable for suspected vascular anomalies. However, it takes longer and is more expensive and hence used sparingly.

Treatment

Surgical drainage is the mainstay of treatment for PTA. Drainage of the abscess can be performed by either needle aspiration or an incision and drainage. Needle aspiration is the most common treatment in the UK.[53] It is relatively pain-free, significantly contributes to pain relief compared with no aspiration[54] and is not associated with any significant complications. However, complete pus drainage may be less reliable than with a quinsy knife thus potentially predisposing to greater recurrence risks and delayed complications. Quinsy knife drainage is mainly used when needle aspiration has failed but it is more painful than needle aspiration and has, historically, been associated with some disastrous complications. Incision and drainage are less painful if carried out with proper infiltration of local anaesthetic at the site of drainage rather than local anaesthetic spray.[54]

Meta-analysis of success rates for needle aspiration gives a rate of 94 with recurrence rates ranging between 10% and 15%.[55] Since recurrence rates with incision and drainage (~10%)[56] are comparable to those with needle aspiration, clinician experience and patient choice should prevail in decision-making regarding the choice of approach.[37]

Medical management

Although surgical drainage is the mainstay of treatment, antibiotics are recommended for resolution of infection. A combination of benzyl penicillin and metronidazole is the preferred choice of antibiotics.[57] In patients with penicillin allergy, erythromycin/clarithromycin should be used. There is some evidence that benzyl penicillin alone is effective,[58] but, in view of the polymicrobial nature of these infections and variable rates of penicillin resistance, a combination of antibiotics is preferred.[37]

The use of steroids as an adjunctive treatment has been increasing, with one RCT reporting a range of favourable outcomes with steroids with no increase in complications.[59] A single dose of intravenous steroid in addition to antibiotic therapy significantly reduces throat pain, time in hospital, fever and trismus.

Supportive management

Attention should be paid towards adequate analgesia for symptomatic relief in this painful condition. Intravenous fluid resuscitation is important in patients who are unable to maintain adequate oral intake.

Inpatient admission for the above measures is the routinely followed practice in UK in the management of PTA. In the US, most patients are managed as outpatients. Multiple studies[56, 60] have shown that patients can be successfully managed in an outpatient setting with high levels of patient satisfaction. Outpatient management of PTA can be recommended if systems are in place for recognition of patients with risk of airway compromise/dehydration, short-term monitoring, good follow-up protocols and easy access for admission if the condition worsens.

Role of tonsillectomy

Abscess tonsillectomy is a technique with a poor reputation in the UK but it is practised in other countries[61, 62] with good results and minimal morbidity, with the additional advantage of avoiding recurrence and the need for

elective delayed tonsillectomy admission.[63] Moreover, the dissection plane is already created by the pus and prevents fibrosis, which makes interval tonsillectomy difficult. In a paediatric population in which needle aspiration or abscess drainage requires general anaesthesia, abscess tonsillectomy under general anaesthesia may be the treatment of choice.[64] Although concerns have been raised about the incidence of post-operative haemorrhage, comparison of the post-tonsillectomy haemorrhage rates of abscess tonsillectomy versus elective tonsillectomy in age- and gender-matched groups shows no statistically significant difference.[62, 65] However, the presence of trismus and associated intubation issues can increase the risk of GA, which has to be weighed against the advantages of the procedure.

Interval tonsillectomy Elective tonsillectomy after recurrent PTA is recommended. Most surgeons do not recommend surgery after one episode alone, as after tonsil-conserving treatments approximately 11% of cases recur by 5 years and 22% by 17–35 years and the number needed to treat would be 5–10 patients. In this group of patients, a subset with a higher risk (20–39 years, recurrent tonsillitis) may be considered for interval tonsillectomy.

Recurrence is rare after the age of 40 and therefore elective tonsillectomy is not warranted.[66]

Deep neck space infections and mediastinitis have been described in 1.8% of cases.[67] Mediastinitis is a condition with significant mortality (23%) [68] even with aggressive management, i.e. combined neck and mediastinal drainage as well as appropriate antibiotic therapy. If initial mediastinal drainage does not lead to resolution, reoperation including contralateral thoracotomy may be required.

Necrotizing fasciitis following PTAs has rarely been described. Treatments advocated include broad-spectrum antibiotics, abscess tonsillectomy and large-scale debridement of necrotic tissue.[69]

Parapharyngeal abscess and retropharyngeal abscess

Parapharyngeal abscess and retropharyngeal abscess are discussed in Chapter 40, Neck space infections.

NON-SUPPURATIVE COMPLICATIONS

Rheumatic fever

Rheumatic fever results from antibodies to streptococcal M protein cross-reacting with heart muscle leading to pancarditis. It may be associated with migratory arthritis involving the large joints, the erythema marginatum rash, subcutaneous nodules, and choreoathetotic movements of Sydenham's chorea. It typically occurs about 1–4 weeks after the GABHS infection.

Elevated or rising antistreptococcal antibody titres provide reliable confirmation of a recent group A streptococcus (GAS) infection and are of value in identifying a preceding GAS infection in a patient suspected of having rheumatic fever.

Although the incidence of rheumatic fever has decreased significantly in the developing world, it is still a major cause of morbidity, with the global prevalence estimated to be at least 15.6 million cases, with 282 000 new cases and 233 000 deaths each year.[70]

POST-STREPTOCOCCAL REACTIVE ARTHRITIS

Post-streptococcal reactive arthritis (PSRA) is a distinct clinical entity following streptococcal infection, with patients presenting with arthritis but lacking other major criteria for diagnosis of rheumatic fever. While the arthritis of rheumatic fever occurs 14–21 days after an episode of GAS pharyngitis and responds rapidly to acetylsalicylic acid, PSRA occurs about 10 days after the GAS pharyngitis and does not respond readily to acetylsalicylic acid.[7]

Post-streptococcal glomerulonephritis

Post-streptococcal glomerulonephritis (PSGN) is a type 3 hypersensitivity reaction and deposition of immune complexes in the glomerulus leading to an acute nephritic syndrome. It usually occurs 1–2 weeks after the infection. Although the incidence of this condition is also decreasing rapidly, it has been estimated that there are more than 470 000 cases of acute PSGN worldwide annually with around 5000 deaths, 97% of them occurring in less-developed countries.[70] Moreover, the majority of acute PSGN in tropical regions occurs predominantly as a result of skin infections, with the burden of PSGN attributable to pharyngitis being much lower. The prognosis for children with acute PSGN is generally favourable with a mortality of <0.5% and fewer than 2% progressing to end-stage renal failure.[71]

Scarlet fever

Scarlet fever is due to exotoxin production (erythemogenic or erythrogenic toxin) and leads to an erythematous rash and the tonsils and pharynx being covered by a yellow membranous film. Desquamation of the papillae of the tongue leads to a 'strawberry tongue' appearance, which is pathognomonic of this condition.

Paediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS)

Paediatric autoimmune neuropsychiatric disorder and acute disseminated encephalomyelitis, which can affect children and adults, have quite recently been recognized as immune-mediated illnesses associated with GABHS infection. Similar to Sydenham's chorea, it is believed to be due to an autoimmune response that cross-reacts with brain tissues and presents as an abrupt onset obsessive-compulsive disorder including hand washing, tic disorders and daytime urinary urgency.

The PANDAS hypothesis has stimulated considerable research, and controversy, but the American Heart Association guidelines state that, based on the current state of knowledge, the concept of PANDAS should be considered only as a yet-unproven hypothesis.[7]

NON-GABHS BACTERIAL PHARYNGITIS

Group C and G streptococci have been noted to be responsible for food-borne and waterborne outbreaks of pharyngitis.[72, 73] Some of these organisms are normal commensals, so differentiating colonization from infection is difficult. They can be cultured in patients with acute pharyngitis with clinical symptoms and examination findings indistinguishable from those of GABHS but generally less severe.[73] Pharyngeal infection with group C and G streptococci can cause acute glomerulonephritis but has never been shown to cause acute rheumatic fever.[74] Penicillin and clindamycin both provide effective eradication when necessary.

Sexually transmitted bacterial infections such as *Neisseria gonorrhoeae* and *Treponema pallidum* can lead to tonsillopharyngeal infections. Anaerobic bacteria can also be copathogens in GABHS infections, with a synergistic effect leading to suppurative complications.

Diphtheria

Diphtheria is a disease which was thought to be almost eradicated in most countries with high levels of vaccination. However, the level of immunity is believed to decline in late childhood and adolescence, depending on the schedule of immunization and the remaining reservoir of the causative organism *Corynebacterium diphtheria* in the population. This fact may lead to gaps in the immunity of the adults and diphtheria outbreaks may occur in subgroups of susceptible individuals despite widespread childhood vaccination.[74]

Diphtheria is caused by *Corynebacterium diphtheriae*, a non-motile, gram-positive pleomorphic bacillus. The characteristic feature is the presence of a fibrinous gray pseudomembrane on the tonsils, sometimes spreading to other areas of the pharynx and larynx, which is usually preceded by sore throat and fever. Attempts to remove the pseudomembrane cause bleeding from the pharyngeal mucosa. Marked cervical lymphadenopathy may lead to the 'bull neck' appearance. Since this condition can rapidly lead to significant airway obstruction or delayed exotoxin-induced myocarditis and neuritis, a high index of suspicion is to be maintained for diagnosis.

DIAGNOSIS

Definitive diagnosis is based on microbiological tests. Culture of swabs is performed on special culture media such as Loeffler medium. Smear morphology shows the classical 'Chinese character' appearance. Confirmation of toxigenicity of the organism was traditionally undertaken by the Elek test, but this test can lead to a delay in diagnosis of more than 48 hours. A rapid immunochromatographic strip (ICS) method for detection of diphtheria toxin has recently been developed.[75] The use of polymerase chain reaction (PCR) for rapid screening of toxigenic *C. diphtheriae* has also been described.[74]

TREATMENT

Treatment consists of rapid administration of antitoxin which can inactivate toxin that has not entered cells. The recommended dose is dependent on the location of the disease and duration of the illness.[51] Antibiotics are also needed to eradicate the organism. Penicillin is the drug of choice and erythromycin can be used as an alternative.

Airway monitoring is important and occasionally intubation/tracheostomy may be necessary to secure the airway. Patients need to be monitored for impending cardiac and neurological complications for up to 3 weeks.

VIRAL PHARYNGITIS

Viral pharyngitis is more common than bacterial and is usually a sequela of the common cold. The viruses that cause common cold (*Rhinovirus, Parainfluenza, Corona*) are the most common etiological agents. Symptoms are similar to those of GABHS pharyngitis, although usually milder, but certain features such as coryza, exanthema and cough are indicative of a viral infection. Treatment is usually symptomatic but can predispose to secondary bacterial infection.

EBV is responsible for the most clinically relevant form of viral pharyngitis, leading to the characteristic picture of IM.

Infectious mononucleosis (glandular fever)

Glandular fever is a common, acute, systemic viral infection presenting typically with the classical triad of sore throat, fever and lymphadenopathy, hence the name glandular fever. The causative agent is the EBV, one of six human herpes viruses isolated from blood, lymph nodes and saliva.

EPIDEMIOLOGY

IM is primarily a disease of young adults but can present in early childhood and older age groups. The current incidence of this condition is estimated at approximately 500 cases/100 000 persons/year with the highest incidence in the age group 15–24 years.[76] Transmission is via saliva, and it has thus been described as the kissing disease. Individuals with the antibody to the viral capsid antigen will not usually develop the disease. The incubation period is normally 5–7 weeks.

CLINICAL FEATURES

There is a prodrome of 4–5 days with malaise, fatigue and headache. The most common symptom is tender cervical adenopathy, usually accompanied by sore throat. Pharyngeal signs range from acute follicular tonsillitis indistinguishable from follicular tonsillitis to a grey membrane lining the oropharynx, petechiae on the soft palate and sometimes a PTA, which can be bilateral (**Figure 51.4**).

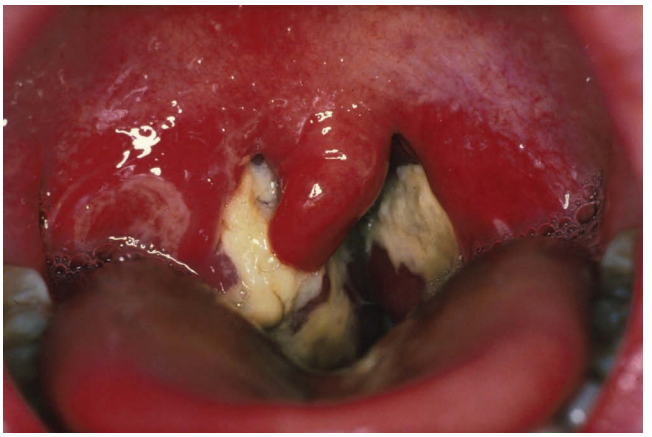

Figure 51.4 Infectious mononucleosis (IM) with features of exudative tonsillitis and false membrane.

Occasionally, all the lymphoid tissue of Waldeyer's ring may enlarge and become covered with a membranous slough, with significant risk of respiratory obstruction. Airway obstruction in IM may be aggravated by herpes infection. Rare, head and neck manifestations include periorbital oedema, especially of the lower lids (Hoagland sign)[77] and cranial nerve mono- and polyneuropathies of which facial nerve weakness is the most common. Other cranial nerves including the hypoglossal nerve, oculomotor nerve and vagus have been reported to be involved either in isolation or as a polyneuropathy.

SYSTEMIC MANIFESTATIONS OF EPSTEIN–BARR INFECTION

The systemic manifestations of EBV infection are summarized in **Box 51.4**.

The oncological risks following EBV-related IM include the following:

- Hodgkin disease
- genome-positive Burkitt lymphoma
- lymphoproliferative disorders in immunocompromised patients
- EBV is a cofactor for the development of nasopharyngeal carcinoma.

Recent developments in molecular and immunological diagnostic approaches have suggested that EBV has a causative role in chronic active EBV infection syndrome, EBV-related haemophagocytic lymphohistiocytosis, EBV genome-positive T-cell lymphoma, natural killer cell leukaemia/lymphoma, Hodgkin disease and gastric carcinoma.

A recent study showed that a history of IM significantly increases the risk of multiple sclerosis.[78]

DIAGNOSIS

The diagnosis is made from the clinical picture, together with the finding of mononucleosis on the peripheral blood film. The two clinical conditions with a similar picture are CMV infection and toxoplasmosis. The differential diagnosis of acute pharyngotonsillitis from IM can be aided by flexible nasendoscopy. Lymphoid tissue is present in the nasopharynx of 92% of patients with IM, unlike in patients with acute tonsillitis. The white cell count may be normal in the first week but is usually raised in the second.

Traditionally, the Hoagland criteria have been used to confirm the diagnosis of IM:[79] at least 50% lymphocytes and at least 10% atypical lymphocytes in the presence of fever, pharyngitis and adenopathy, and confirmed by a positive serological test.

It has recently been suggested that a lymphocyte/WBC ratio could be a quick screening tool to differentiate acute tonsillitis from glandular fever.[80] This study concluded that a ratio higher than 0.35 could indicate glandular fever. However, a review of this hypothesis by a large retrospective study involving 1000 individuals who underwent a monospot test revealed that this ratio had a sensitivity and specificity of only 72% and 84% respectively for the detection of this condition.[81] The authors concluded that, although it is a good indicator of IM, using this ratio alone would lead to one in seven of the patients with IM being missed. It has therefore been proposed that the L/WCC ratio should only be used in conjunction with the Hoagland criteria.

BOX 51.4 The systemic manifestations of EBV infection

Common	Rare
Pyrexia usually accompanies the severe form of the disease	Gastrointestinal: acute appendicitis, mesenteric adenitis, pseudoappendicitis
Generalized lymphadenopathy	Genitourinary: genital ulceration, interstitial nephritis
Splenomegaly occurs in 50% of patients with occasional reports of rupture following blunt soft-tissue trauma or splenic infarcts	NS: Guillain–Barré syndrome, meningoencephalitis, myelitis
Hepatomegaly and jaundice occur in 10% of patients and liver function tests are frequently abnormal	CVS: myocarditis, infective endocarditis, pericarditis
Ascites	RS: pneumonitis, bilateral empyema and mediastinitis
Rubelliform skin rash sometimes occurs and almost invariably if ampicillin is prescribed	Haem: severe autoimmune haemolytic anaemia, haemophagocytic syndrome aplastic anaemia and thrombocytopenia and common variable immune deficiency
	Chronic fatigue syndrome following IM with a premorbid history of poor physical functioning being the main predictive factor. The risk of chronic fatigue syndrome postglandular fever has been estimated to be 9–22% 6 months after glandular fever compared with 0–6% following an ordinary URT infection. EBV virus infection may have a role in initiating multiple sclerosis
	Unexpected deaths possibly related to upper airway obstruction

The heterophil antibody test has remained the basis for serological diagnosis since 1932 when Paul and Bunnell discovered that serum from IM patients caused sheep erythrocytes to agglutinate. The monospot test, which uses bovine erythrocyte-extracted antigen to detect heterophil antibodies, is the most commonly performed serological test today. Both of these are screening tests. The sensitivity of this test varies from 63% to 95% whereas the specificity varies from 84% to 100%, based on the various commercial kits available.[82] False positive monospots can occur in healthy controls as well as in a variety of conditions including mumps, systemic lupus erythematosus, Mediterranean spotted fever and diabetes sarcoidosis. These tests are usually positive in the first week of the disease, although approximately 10% never develop a positive test and this figure may be higher in children. Serological tests cannot distinguish between typical and atypical severe forms of IM.

The gold standard includes serological evidence of EBV-specific antibodies, the most useful being immunoglobulin M (IgM) antibody to EBV viral capsid antigen found during acute primary EBV infection. A recent review of new diagnostic modalities suggested that real-time PCR and measurement of EBV viral load may aid in the early diagnosis of IM in cases of inconclusive serological results.[82]

Female patients without tonsillitis and a WCC of less than 10 and an aspartate aminotransferase over 150 are at significant risk of complications and should be carefully monitored.

TREATMENT

Treatment is symptomatic for mild to moderate cases.

Role of antivirals

A lot of interest has been generated in the role of antivirals in treating this condition. Acyclovir (ACV) is the most commonly prescribed antiviral agent. A meta-analysis of five RCTs involving 339 patients with IM treated with ACV concluded that clinical data did not justify use of ACV for the treatment of mild to moderate IM.[85]

On the other hand, there is evidence to suggest that antiviral agents may benefit patients with severe manifestations of IM, especially when used as an adjunct to corticosteroids.[86] This may be increasingly justified for some of the high-risk complications and prolonged fatigue syndromes.

Ampicillin-based antibiotics should be avoided because of the certainty of producing a rubelliform rash.

Role of steroids

The role of steroids is similar to that of antivirals. A Cochrane review concluded that there was insufficient evidence to recommend steroids for routine symptom control in IM.[87]

However, steroids have been indicated in the setting of acute upper airway obstruction secondary to this condition. The role of corticosteroids in managing complications other than upper airway obstruction is less clearly defined but there may be a role in immune-mediated anaemia, thrombocytopenia and interstitial nephritis.

Patients who develop upper airway obstruction seem to be more prone to developing later recurrent tonsillitis, and acute tonsillectomy has the incidental benefit of avoiding this complication. Rarely, tracheostomy may be required if tonsillectomy fails to relieve airway obstruction.

Contact sports should be avoided for 4–6 weeks even in the absence of splenic enlargement because of the risks of splenic rupture.

There is ongoing research regarding the role of novel therapeutic agents including 5-substituted uracyle, azacytosine derivatives, and peptides inhibiting EBV-mediated membrane fusion in the management of IM.[82]

Cytomegalovirus

Cytomegalovirus (CMV; herpes virus 5) is ubiquitous, and most individuals develop antibodies to it due to infection in childhood. Infection in the immunocompetent host rarely results in clinically apparent disease. Infrequently, immunocompetent hosts exhibit a mononucleosis-like syndrome with mild pharyngitis. About two-thirds of adults with heterophil-negative mononucleosis have CMV-induced mononucleosis. Patients with this illness are usually older than those with EBV IM. Symptoms are similar to IM but lymphadenopathy is less common. The diagnosis is made by isolating CMV from the blood or showing a fourfold rise or greater in antibody titre to CMV.

The virus can lead to a significantly more severe infection in immunocompromised hosts, especially in those with HIV infection.

Herpes simplex 1

Type 1 herpes simplex infection primarily involves the oral cavity and oropharynx and usually affects young children, being less frequently found in the late teens and early twenties. It causes severe vesicular and ulcerative stomatitis of the lips, tongue, gums, buccal mucosa and, occasionally, oropharynx. The oropharyngeal involvement may be an isolated pharyngitis without ulceration or vesicles. Children are systemically unwell with pyrexia, tachycardia and cervical adenopathy.

Diagnosis is usually clinically obvious, although it may be confused with Stevens–Johnson syndrome. The condition is infective and may be transmitted to staff. Occasionally, severe ulcerative pharyngitis may be due to type 2 herpes simplex infection contracted by heterosexual orogenital contact. In the virology laboratory virus from an unruptured vesicle can be identified using fluorescent antibody or be seen as intranuclear inclusions on scrapings. Secondary herpetic infection takes place when the herpes virus resides within the posterior root ganglion. Intercurrent illness then results in the appearance of herpetic vesicles, usually in the lips or the angle of the mouth, as a typical cold sore.

The treatment is usually supportive with appropriate analgesics and fluids. Acyclovir is active against herpes virus but does not eradicate it. It is effective only if started at the onset of infection.

Herpes zoster

Herpes zoster pharyngitis probably arises from the reactivation of virus particles in the cranial nerve nuclei after a previous attack of chickenpox, thus it is analogous to shingles or cold sores. It can, though, also appear during an epidemic of chickenpox. In the pharynx, herpes zoster can materialize in the distribution of the Vth, IXth and Xth cranial nerves. It often occurs with herpes zoster oticus (Ramsey–Hunt syndrome). The pharyngeal features may be transient and can easily be overlooked. They may give rise to pain on swallowing, vesicles and shallow ulcers, which heal rapidly, may be seen on the soft and hard palate, tonsil or posterior pharyngeal wall.

Treatment with antivirals should be started within 72 hours of onset of the lesions. Acyclovir has been the drug of choice in the past, but newer drugs such as valacyclovir and famciclovir are equally effective and have more convenient dosing regimens and decreased incidence of post-herpetic neuralgia. A single dose of gabapentin reduces acute pain associated with herpes zoster infection. Herpes zoster vaccination markedly reduces the incidence and morbidity of this condition as well as the likelihood of developing post-herpetic neuralgia.

Hand, foot and mouth disease

This is usually caused by enterovirus 71 or coxsackieviruses, but untypable enteroviruses and mixed cultures may also be responsible. It is characterized by a vesicular eruption in the oral cavity and oropharynx causing dysphagia and dehydration, accompanied by vesicles on the hands and feet. It is normally accompanied by pyrexia, malaise and vomiting. The illness is short-lived and mainly affects young children but has been associated with mortality, for example in the 1998 epidemic in Taiwan. Fulminant enterovirus 71 infection may lead to severe neurological complications, acute pulmonary embolus and cardiopulmonary decompensation. Age younger than 3 years has been associated with higher mortality as have larger families and kindergarten attendance. Hospital admission, careful staging and stage-based management reduce the fatality rate in those with cardiac complications. Initial investigations include stool cultures and a white blood cell count. Currently, hand, foot and mouth disease is not susceptible to antiviral agents or vaccination, and prevention of outbreaks in high-risk areas requires high-level surveillance and public health interventions.

Herpangina

This is a self-limiting vesicular eruption that occurs in the oropharynx and a number of enteroviruses (30 and 71) and coxsackievirus group A have been implicated. Its regular spread to the oropharynx distinguishes it from herpes simplex type 1 infection.

NON-SPECIFIC CHRONIC PHARYNGITIS

Non-specific chronic pharyngitis is a common clinical diagnosis and relies on a history of long-standing throat discomfort of variable severity without any evidence of specific aetiological factors, with often little to find on clinical examination apart from prominent lymphoid tissue, especially lateral pharyngeal bands. Possible aetiological factors include:

- heavy smoking, including passive smoking
- industrial/occupational irritants
- chronic sinusitis with post-nasal drip
- acid reflux
- poor dental hygiene
- psychological stress
- *Chlamydia pneumoniae* infection
- indoor secondary heating sources (which emit NO_2 and SO_2).

Exclusion of malignancy is the most important aspect of managing these patients. This requires a careful history, in particular enquiring about localized pain to one side and earache, progressive dysphagia or weight loss, and careful physical examination of the whole upper aerodigestive tract with a nasendoscope and otoscopy. Direct examination of the oral cavity and oropharynx, paying special attention to the tongue, floor of the mouth, buccoalveolar sulcus region and manual palpation of the tongue, including its base, is required. Finally, the neck must be carefully palpated to exclude lymph node metastases. Usually this is sufficient to exclude malignancy in the absence of unexplained otalgia or progressive dysphagia but, occasionally, further investigations, mainly rigid panendoscopy under general anaesthetic to take biopsies, may be required.

If physical examination bears out evidence of post-nasal drip or significant acid reflux, both should be treated appropriately with intranasal steroids and proton pump inhibitors, although there is little documentation to support this practice.

Strong advice is given about cutting out smoking and alcohol if these are involved and an appropriate dental referral may need to be initiated. In those patients where stress is deemed to be a significant factor, neck and throat muscle relaxation therapies are deemed to be beneficial.

A large variety of non-specific remedies has been used, such as gargles, antiseptic and analgesic throat spray, with no well-defined benefits. Surgery is of no demonstrable help in this situation and operations to remove excess extratonsillar lymphoid tissue are of no proven benefit.

SPECIFIC CHRONIC PHARYNGITIS

Syphilis

This is an infection by the spirochaete *Treponema pallidum* and, apart from the congenital form, is acquired

through sexual intercourse. The disease progresses through primary, secondary and tertiary stages with the secondary stage being most likely to give rise to pharyngeal symptoms. The condition may present with almost any symptom in any organ system and hence is termed the 'the great pretender'. The lesion of primary syphilis is at the site of initial inoculation and the organism can penetrate both normal and mucosal abrasions. After a decade of unprecedented decline in the 1990s, the worldwide incidence of syphilis has been rising since 2000, mainly among HIV-positive men. This has been well-documented in the UK.[88] Patients immunocompromised by HIV have a higher likelihood of developing neurosyphilis.

In primary syphilis, the lesion is the chancre, which develops after an incubation period of 21 days. The most frequent extragenital sites for the chancre are the lips, tongue, buccal mucosa and tonsil. The lesion begins as a papule that breaks down to form a painless ulcer with indurated margins. At the same time there may be non-tender uni- or bilateral cervical lymphadenopathy. Secondary infection of the classically painless ulcer can result in pain. The ulcer usually persists for 2–6 weeks and then heals spontaneously, often despite inappropriate treatment. While the primary lesion is present the patient is highly contagious. It is therefore very important to consider the possibility of primary syphilis in atypical oral or oropharyngeal ulceration.

Secondary syphilis usually occurs several weeks (commonly 4–6 weeks) after the primary lesion and about 30% of patients at this stage will have a healing chancre. The features of the second stage are fever, headache, malaise, generalized lymphadenopathy, mucocutaneous rash and sore throat. The pharynx and soft palate display hyperaemia and inflammation and there may be lesions, which have been described as mucous patches or 'snail track' ulcers. The lesions are more commonly seen in the oral cavity than the oropharynx and are ulcerated and covered with a greyish white membrane, which when scraped off has a pink base with no bleeding. The secondary stage of the disease lasts a few weeks and, again, the lesions in the mouth and pharynx are infectious. About 30% of cases will go on to develop the tertiary stage.

Tertiary syphilis develops 5–25 years after the initial infection and is characterized by lesions that may be widespread throughout the body or restricted to one or two organ systems. In the URT they are due to gumma. This is a granulomatous necrotic lesion that begins as a nodule and then breaks down to form an ulcer. It can arise in the hard palate, nasal septum, tonsil, posterior pharyngeal wall or larynx. The gumma, whether ulcerated or not, is typically painless. There is usually no lymphadenopathy unless the lesions are secondarily infected. When treated with penicillin, the gumma will heal rapidly.

DIAGNOSIS

In the primary or secondary stage of the disease, spirochaetes can be identified by darkfield illumination microscopy in smears taken directly from the lesion. PCR may be used on oral or other lesions where contamination with commensal treponemes is likely. The spirochaetes can also be identified in biopsy specimens using silver stains or fluorescent-labelled antibody. Biopsy of a tertiary lesion provides a typical histopathological picture.

Serological tests for syphilis fall into two main groups: those used to identify non-specific antibodies to cardiolipin (i.e. Venereal Disease Research Laboratory (VDRL)/rapid plasma reagin (RPR) tests) and those to detect specific treponemal antibodies.

There are several tests to detect specific treponemal antibodies. The UK national guidelines[89] recommend using treponemal enzyme immunoassay (EIA) to detect immunoglobulin M and immunoglobulin G (IgG), if primary syphilis is suspected. IgM is detectable towards the end of the second week of infection while IgG is detectable usually in the fourth or fifth week. A positive screening test should be confirmed with a different treponemal test. The other tests include *T. pallidum* haemagglutination assay (TPHA), *T. pallidum* particle agglutination assay (TPPA), fluorescent treponemal antibody absorbed test (FTA-ABS) and *T. pallidum* recombinant antigen line immunoassay. All the specific tests are almost invariably positive in secondary and early latent syphilis.

The guidelines recommend that a quantitative VDRL/RPR test should be performed when treponemal tests indicate syphilis, as this helps stage the disease and indicates the need for treatment. The VDRL tests use an antigen extracted from beef heart in a slide flocculation test. The VDRL reaction starts to become positive during the first or second week after the development of the chancre and 99% of patients with secondary syphilis have a positive reaction.

An immunoblot (*T. pallidum* recombinant antigen line immunoassay) is recommended when the standard confirmatory test does not confirm the positive treponemal screening test result.[90]

TREATMENT

Penicillin is the treatment of choice, with 2.4 mega units i.m. in single or divided doses, being the standard for primary and secondary syphilis. In tertiary syphilis, 7.2 mega units in divided doses of 2.4 mega units at 7- to 14-day intervals are recommended. Azithromycin is recommended as a second-line alternative in primary syphilis.

Full details of treatment regimens can be obtained from the detailed guidelines on the management of early and late syphilis.[89]

Tuberculosis

The pharynx is not a common site for clinically manifest tuberculosis (TB); however, it is the site of primary infection almost always in children and results in an asymptomatic primary focus in the pharynx (usually tonsil or adenoid) with cervical lymphadenopathy.

Secondary TB affects the pharynx, but only in patients with massive positive and usually cavitating pulmonary TB. This is in contrast to laryngeal TB in which lesions do

occur with low-grade or inactive pulmonary disease. The pharyngeal lesions are secondary to coughing up heavily infected sputum and consist of multiple, painful shallow ulcers in the pharynx or oral cavity. Occasionally, the pharynx is involved in patients with widespread military TB and here the lesions may be from blood-borne as well as sputum-borne dissemination of disease. Lupus vulgaris is a low-grade cutaneous form of TB and has been described in the nasal cavities and in the pharynx. Tuberculous otitis media is probably a blood-borne dissemination of the disease but, on occasion, can result from pharyngeal disease by spread from the Eustachian tube.

The resurgence of TB has closely paralleled the epidemic caused by HIV. In both the US and Africa, the areas with the highest rates of HIV infection and high-risk groups, such as intravenous drug abusers, are those that have sustained the highest increase in TB. Poverty, overcrowding and homelessness are the socioeconomic factors common to coinfection with both. HIV-infected individuals are at risk of reactivation of previous TB and to rapid progression of acquired infection. The presentation is often atypical and an increase in extrapulmonary TB has been demonstrated.

DIAGNOSIS

The diagnosis is usually clear because of the association with pulmonary disease, both clinically and radiologically, although pharyngeal squamous cell carcinoma with pulmonary metastases is the obvious differential. Microscopic examination of stained smears for acid-fast bacilli is still one of the most useful tests for the initial diagnosis of TB. Although less sensitive and specific than culture, the sensitivity can be greatly improved by using phenol auramine stain as compared with the older Ziehl–Neelsen technique. Semi-automated and continuous monitoring systems developed specifically for the isolation of mycobacteria include enzyme-linked immunosorbent assay (ELISA) tests to detect antigens and PCR to detect genetic elements.

TREATMENT

Pharyngeal TB requires no special treatment. It will, in principle, be treated at the same time as the pulmonary disease with triple therapy, usually isoniazid, rifampicin and pyrizinamide as first-line drugs. All cases should be treated in association with an interested specialist. Drug resistance (DR) worsens outcomes and may have significant cost implications. Multiple drug resistance (MDR) is found globally. Management relies upon treatment with at least three drugs to which the isolate is susceptible. Directly observed treatment strategy should be used in adults and children where there is a significant risk of non-compliance and is vital to cut down transmission of disease in the community. TB can be controlled if appropriate policies are followed, effective clinical and public health management is ensured, and there are committed and coordinated efforts from within and outside the health sector. Rapid expansion of effective TB control services is urgently required to avert the continued high burden of morbidity and mortality from TB and its effects on the HIV pandemic.

Toxoplasmosis

Toxoplasmosis is a common disease of birds and mammals caused by the protozoan *Toxoplasma gondii*, which was first described in 1908. The parasite has three stages in its life cycle: tachyzoite, oocyst and tissue cyst. The infection can be transmitted to humans (zoonosis) by the ingestion of cysts or food contamination with animal faeces, the incorporation of tissue cysts or tachyzoites from transplanted organs or blood products from other humans with acute or latent toxoplasmosis, and transplacental transmission from a mother who is acutely infected. About 750 cases of toxoplasmosis occur annually in the UK with a mean age of 30 years. The number of cases rises evenly from adolescence with males predominating up to the age of 20 but after this age females prevail. The age distribution has rose over the 1980s. There is no longer any seasonal or geographical distribution.

In immunocompetent humans, acquired toxoplasmosis usually gives rise to no symptoms. Some patients have a sore throat with malaise, fever and cervical adenopathy and, on occasion, a patient will present with cervical lymphadenopathy only. The fever and malaise may last for several weeks and many organ systems, such as lungs, skin, liver, spleen, myocardium, pericardium, liver, brain, eyes and skeletal muscles, may be involved. The disease is usually self-limiting; rarely, symptoms persist for many years due to chronic active infection, but death is most unusual. The differential diagnosis is usually from other glandular fever-type syndromes. Eye disease presents as isolated retinochoroiditis with little systemic or immunological response. Transplacental infection occurs in approximately 45% of women who acquire toxoplasmosis during pregnancy. The effects range from subclinical infection to intrauterine death. Damage to the central nervous system and retinochoroiditis are the most common nonfatal affections. Only 10–20% of congenitally infected infants have clinically apparent disease at birth but most will develop some sequelae in later life, most commonly retinochoroiditis.

Toxoplasmosis in people with impaired immunity has been documented in association with cancer, organ transplantation, connective tissue disorders and HIV infection. Patients with such conditions are more likely to experience reactivation of latent disease than to acquire new infections. Encephalitis and space-occupying lesions in the brain may develop and, if untreated, rapidly progress to disseminated infection.

DIAGNOSIS

The differential diagnosis is usually from other glandular fever-type syndromes. A dye test for the serological diagnosis of toxoplasmosis was described in 1948. This test, in modified form, remains the gold standard although for diagnostic purposes it is restricted on grounds of cost to

reference laboratories. Several tests for specific antibody classes have been developed and used for diagnostic as well as epidemiological purposes. Lymph node biopsy, which reveals follicular hyperplasia and typical epithelioid cells, is sometimes carried out to confirm the diagnosis.

TREATMENT

Treatment is usually unnecessary but in those individuals with severe systemic upset or immunodeficiency a combination of pyrimethamine and sulphadiazine is indicated, although these are associated with significant side effects. A combination of primethamine and azithrimycin with similar efficacy but fewer side effects has been used for sight-threatening ocular toxoplasmosis. A twice weekly, 25 mg pyrimethamine/500 mg sulphadoxine combination is used as effective prophylaxis against toxoplasmosis encephalitis and *Pneumocystis carinii* pneumonia in patients with advanced HIV infection. In an effort to minimize side effects, considerable work is ongoing to develop new drugs or drug combinations for the treatment of severe symptomatic toxoplasmosis. Early studies suggest that macrolides and fluoroquinolones are possibly effective. A Cochrane review demonstrated a lack of evidence for routine treatment of the acute form of toxoplasma retinochoroiditis but weak evidence for treating chronic disease.

Leprosy

Leprosy is a rare condition in the UK, a dozen or so cases per year notified since the 1990s. No definite cases of indigenously acquired leprosy have been reported since the disease became notifiable. Globally, of the 122 countries considered endemic for leprosy, WHO states that 119 have eliminated the disease as a public health problem (defined as 1 case per 10 000).[90] It is a curable, chronic infectious disease caused by the bacillus *Mycobacterium leprae* that mainly affects the skin and peripheral nerves but also the respiratory mucosa and eyes. Leprosy affects all ages and both sexes. It is still a stigmatizing disease and yet, despite its reputation, is not a highly infectious one. Prolonged contact with an untreated person suffering from an infectious form and an inherent immunological susceptibility in the exposed person are normally required for transmission to take place.

Leprosy usually begins as an anaesthetized area in a hypopigmented skin lesion that can arise anywhere within the body. The spectrum of disease that then develops depends upon the degree of cell-mediated immune response mounted by the host. If there is a vigorous host response, tuberculoid leprosy, which is not infectious and clinically must contain fewer than five skin lesions, results. Borderline leprosy can progress to lepromatous leprosy with numerous skin lesions and this is infectious.

Isolated leprosy of the pharynx does not occur. It spreads to the naso- and occasionally oropharynx from the nasal cavities. Lepromatous leprosy can affect the pharynx and gives rise to a combination of granulomatous lesions ulcerating and healing with fibrosis.

DIAGNOSIS

The diagnosis is usually made by biopsy.

TREATMENT

Treatment is with multidrug chemotherapy, which was introduced by WHO in 1982.[91] Under this programme, patients are classified as having one of two types – paucibacillary (PB) or multibacillary (MB) – and receive either the combination of rifampicin and dapsone (known as paucibacillary multidrug therapy or PB-MDT) or the triple drug combination of rifampicin, dapsone and clofazimine (known as multibacillary multidrug therapy or MB-MDT). The rifampicin and part of the clofazimine component are taken monthly under supervision. PB-MDT is given for 6 months and MB-MDT for 1–2 years.[92] Chemoprophylaxis with dapsone and Bacille Calmette-Guérin (BCG) vaccine provide protection for household contacts.

Scleroma

Scleroma is a chronic infective condition caused by *Klebsiella rhinoscleromatosis*. The disease begins in the nose and only secondarily spreads to the pharynx where it produces granulomatous lesions and scarring.

Candidiasis

Oropharyngeal candidiasis (OPC), or thrush, is a common infection typically caused by the yeast *Candida albicans*, which is part of the flora of the oral cavity and oropharynx in 30% of normal individuals. Other *Candida* species such as *C. glabrata*, *C. krusei*, *C. tropicalis*, *C. parapsilosis* and *C. dublinensis* have also often been implicated, especially in immunosuppressed individuals.

In order for these organisms to become pathogenic and symptomatic there must be some local or systemic change in the host. The predisposing factors are listed in **Box 51.5**.

CLINICAL FEATURES

Clinically, candidiasis may be asymptomatic or present with pain and dysphagia. Examination reveals small

BOX 51.4 Predisposing factors for candidiasis

Local	Systemic disease and or immune compromise
Local disease: lichen planus, leukoplakia	Diabetes mellitus
Systemic antibiotics may change local oral flora sufficiently to allow overgrowth of *Candida*	Lymphoma
Radiotherapy to the oral cavity and oropharynx	Immunosuppressive drugs
	AIDS
	Usually *C. albicans*, but increasingly *C. dubliniensis* is becoming the opportunistic infective agent

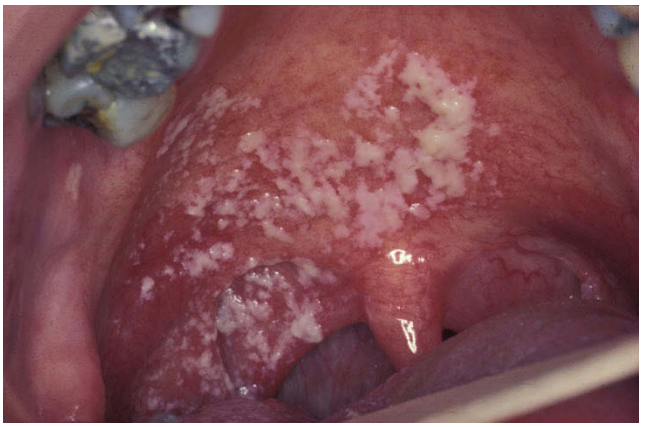

Figure 51.5 White membranous lesions of the soft palate in a man who uses steroid inhalers. This appearance is typical of pseudomembranous candidiasis.

white/creamy-white plaque-like lesions on the tongue, palate, buccal mucosa or oropharynx (pseudomembranous lesions). These can typically be 'wiped' away from the underlying mucosa to leave an erythematous ulcer or an erythematous lesion (**Figure 51.5**). The presentation could also be in the form of chronic hyperplastic candidiasis (i.e. hyperkeratotic white patch), which cannot be removed by scraping or chronic atrophic candidiasis (i.e. erythema without plaque formation).

TREATMENT

Mild disease responds well to local therapy, such as nyastatin drops or lozenges 100 000 units 6-hourly, or clotrimazole troches at a dosage of 10 mg five times daily and there is little risk of developing resistance. For moderate to severe disease, oral fluconazole at a dosage of 100–200 mg (3 mg/kg) daily for 7–14 days is recommended.[93]

Increasing resistance of *Candida* species to fluconazole is becoming a problem, especially in the HIV population. For fluconazole-refractory disease, either itraconazole solution or posaconazole suspension can be used.[93] In severe cases not responding to triazoles, a new class of agents called echinocandins or amphotericin may rarely be required.

Neither primary nor secondary prophylaxis is recommended for most patients exhibiting OPC because of the potential for resistant *Candida* species to develop over time with continued antifungal pressure.[94] Moreover, mucosal disease is associated with very low attributable morbidity and mortality, and acute therapy is highly effective.[95]

HIV and AIDS

Although great progress has been made in the global response to the AIDS epidemic in 30 years, more than 34 million people are still living with HIV infection worldwide.[96] Sub-Saharan Africa continues to be the most affected continent, followed by Eastern Europe and the Caribbean.

Pharyngeal presentation of HIV disease includes the following:

- acute seroconversion illness
- opportunistic infections, especially with *Candida*, but also TB, syphilis, CMV and *Cryptococcus*
- oral hairy leukoplakia (OHL) and Kaposi's sarcoma (KS), both AIDS-defining illnesses, and oral aphthous ulceration
- lymphoid tissue hyperplasia
- neoplastic lesions including non-Hodgkin lymphoma (NHL), KS, SCC of the head and neck, Hodgkin disease, myeloma and leiomyosarcoma in children.

PRIMARY HIV INFECTION/ACUTE SEROCONVERSION ILLNESS

Primary HIV can be asymptomatic or result in severe symptomatic illness. Common symptoms are pyrexia, pharyngitis, malaise, lethargy, maculopapular rash, mucous membrane ulceration, cervical lymphadenopathy and headache. Non-head and neck manifestations of primary HIV infection might include gastrointestinal tract transit disturbances, weight loss, anorexia, abdominal pain, myalgia, arthralgia and neurological features. The differential diagnosis is with glandular fever-type syndromes. A careful sexual history may provide a clue. It can be diagnosed by virology testing (HIV-1 RNA level >50 000 copies/mL) in the absence of HIV-specific antibodies (ELISA and confirmatory Western blot antibody testing). Progression to late-stage disease is influenced by the severity of the symptoms in primary HIV infection, the duration of illness, and the presence of neurological symptoms and oral candidiasis. Currently, the experimental evidence is insufficient to recommend whether those diagnosed with primary HIV infection should routinely receive antiretroviral therapy although it is routinely given in the US. Treatment of primary infection with highly active antiretroviral therapy (HAART) does not prevent establishment of chronic infection. Very early therapy could, potentially, decrease the viral set point, prevent viral diversification, preserve immune function, improve clinical outcome and decrease secondary transmission.

ORAL AND OROPHARYNGEAL LESIONS DUE TO OPPORTUNISTIC INFECTION

Oral candidiasis has been reported as the most prevalent oral lesion. *Candida* species other than *Candida albicans* are more prevalent in HIV disease, including *C. glabrata, C. krusei* and *C. dubliniensis*. Fluconazole is the mainstay of therapy, although resistance is developing. *Penicillium marneffei*, a newly described fungal infection, has been identified in South East Asia.

Oral lesions common in the early years of the AIDS epidemic including KS, oral aphthous ulceration, AIDS-associated oral lymphoma (Figure 51.6) and OHL all contain EBV DNA. Abundant viral replication only occurs in OHL and is due to a previously unknown mechanism involving concurrent expression of prolific, replicative

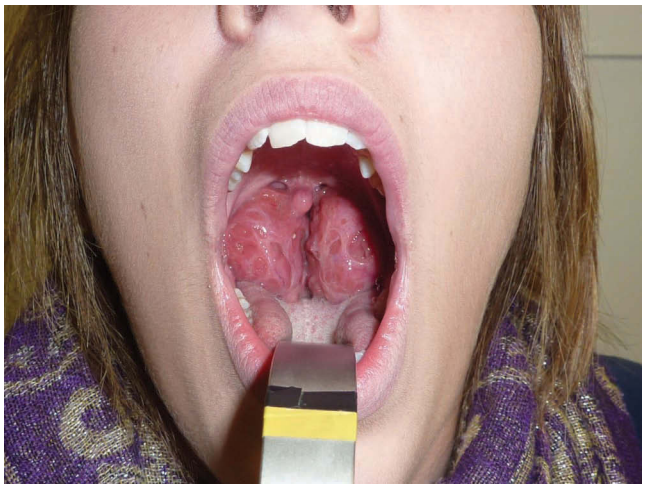

Figure 51.6 Tonsil hypertrophy presenting as lymphoma in an immunocompromised patient.

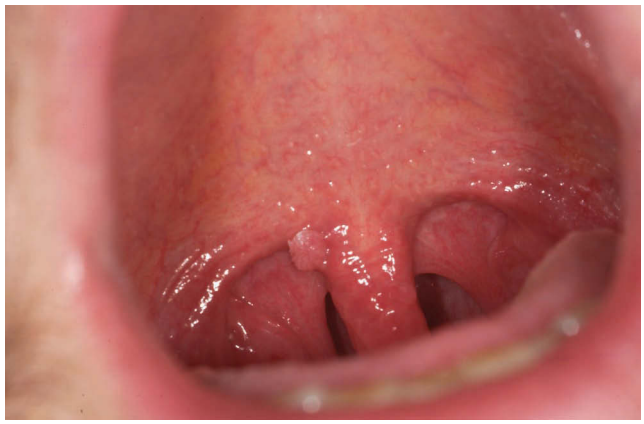

Figure 51.7 Papilloma on the uvula seen as a discrete papillary, cauliflower-like lesion.

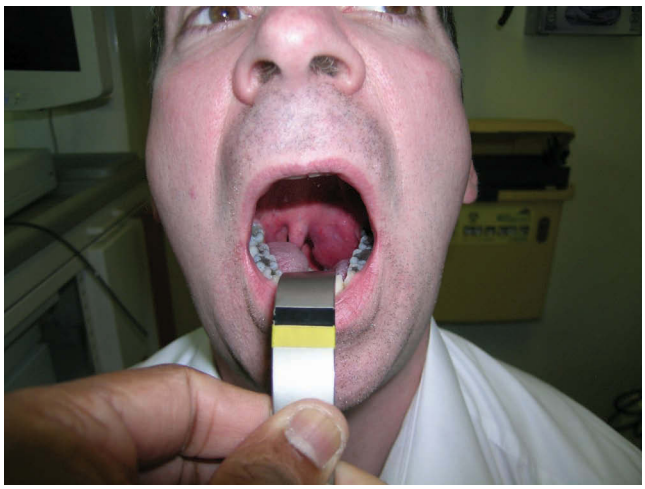

Figure 51.8 Lymphoid tissue hyperplasia.

and transforming proteins of the gamma herpes virus EBV. KS has also been shown to contain a different herpes virus specific to this lesion, which is now known as KS-associated virus.

Oral lesions, especially pseudomembranous and/or erythematous candidiasis and OHL, which are highly suggestive of HIV infection in individuals of unknown HIV status and those known to be HIV infected, indicate that the battle lines between HIV virion production and destruction of immunologically important cells have been drawn. These observations have led to the almost universal inclusion of oral lesions in HIV staging. Recently, lower frequencies of oral disease due to HAART have been noted, except that oral warts may become more common as the viral load falls and the CD4 count rises. Human papillomaviruses (HPV) are associated with oral warts in HIV-positive individuals (**Figure 51.7**), a diagnosis that is increasing. Types include verruca vulgaris, condyloma acuminatum and focal epithelial hyperplasia. In addition to HPV, herpes simplex virus infection is increasing in this group and may run an atypical course including presentation as an exudative erythema multiforme. In children with HIV infection, additional oral lesions include angular cheilitis, ulcerative gingivitis/periodontitis and enamel hypoplasia, salivary gland disease, linear gingival erythema over-retention and delayed primary eruption of teeth. OHL is much less common in children than adults.

LYMPHOID TISSUE HYPERPLASIA IN THE PHARYNX

Lymphoid tissue hyperplasia (**Figure 51.8**) in the pharynx commonly involves all the tissues of Waldeyer's ring including adenoidal, palatine and lingual tonsils. Adenoidal hyperplasia and hypertrophy may cause Eustachian tube obstruction and otitis media with effusion. Biopsy of this tissue to exclude nasopharyngeal carcinoma and lymphoma is mandatory but radical adenotonsillectomy is to be avoided because of the bleeding risks. HIV viral RNA but no other microorganisms can be identified in this tissue. The complex immunological changes suggest that HIV may be disseminated through the upper aerodigestive tract via target cells. Subsequent presentation of viral antigens to the tonsillar and adenoidal lymphoid tissue results in simulated neoplastic proliferation of these structures, which are highly suspicious of HIV, even in asymptomatic HIV-positive patients.

PHARYNGEAL NEOPLASMS

Pharyngeal neoplasms include KS, NHL and SCC. The outlook for patients with these malignancies has improved significantly with the use of HAART and more aggressive cytotoxic therapies. The relative risk of acquiring these conditions compared with non-HIV-infected individuals is for KS greater than 10 000, B-cell NHL greater than 100, NHL eight and multiple myeloma five. Children also have a high risk of leiomyosarcoma (RR = 10 000). KS appears to result from an uncontrolled expression of latency genes of human herpes virus-8. It is exquisitely sensitive to immune deficiency and its incidence has declined rapidly with the use of HAART while

that of NHL has declined much less so. Patients with head and neck SCC who are HIV-positive in the absence of AIDS, presented at a younger age, more frequently experienced treatment-related complications and had a poorer outcome, suggesting that head and neck SCC may be an AIDS-defining diagnosis. Oral cavity and oropharyngeal tumours in HIV-positive patients respond to radiation therapy but there is a marked difference in the degree of acute reactions to treatment between patients with and without KS.

BEST CLINICAL PRACTICE

- ✓ A combination of Centor Clinical prediction score and Rapid Antigen Detecton test (RADT) should be used to diagnose GABHS pharyngitis.
- ✓ Supportive care with NSAIDs/Paracetamol with delayed antibiotics (48 hours after presentation) or no antibiotics for most patients with GABHS pharyngitis.
- ✓ SIGN guidelines[4] as a criterion for tonsillectomy.
- ✓ Serum Monospot test for patients with suspicion of Infectious mononucleosis.
- ✓ HIV infection to be considered in unusual pharyngeal presentation.

FUTURE RESEARCH

- ➤ Quality-of-Life studies to further ascertain the role of tonsillectomy in adults.
- ➤ Selective vs. Universal use of RADT in patients with pharyngitis.
- ➤ Role of novel therapeutic agents in the management of infectious mononucleosis.

KEY POINTS

- Viruses and not bacteria are the most common cause of acute sore throat, but GABHS is still the most frequent bacterial pathogen.
- Despite some forms of acute pharyngitis being associated with classical presentations, one cannot reliably distinguish between viral and bacterial aetiologies on clinical grounds alone.
- In UK practice there is insufficient evidence to support the use of antibiotics in the management of acute sore throat for symptom relief and prevention of spread, recurrent sore throat or to prevent rheumatic fever, glomerulonephritis or suppurative complications.
- The indications for tonsillectomy in the setting of recurrent/chronic tonsillitis/pharyngitis are controversial with varied opinions regarding the relative risks and benefits. The referral criteria currently used in the UK are based on the SIGN guidelines.
- There has been a steady increase in the incidence of peritonsillar abscess over the past 10 years. Drainage of abscess can be performed either by needle aspiration or an incision and drainage.
- Pharyngeal signs of EBV infection are clinically indistinguishable from follicular tonsillitis and even PTAs may occur as a complication. Screening tests include the monospot and Paul Bunnell tests, but both have false-positives rates. EBV IgM to viral capsid antigens is the gold standard for accurate diagnosis. Treatment is symptomatic in most cases but antiviral agents may be justified in the presence of systemic complications.

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CHAPTER 52

CRICOPHARYNGEAL DYSPHAGIA

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SEARCH STRATEGY

Data in this chapter are based on a Medline search using the keywords: upper oesophageal sphincter, oropharyngeal, dysphagia, cricopharyngeus/cricopharyngeal, pharyngeal pouch, hypopharyngeal diverticulum and Zenker's diverticulum.

INTRODUCTION

This chapter is about difficulty swallowing due to dysfunction of the upper oesophageal sphincter or cricopharyngeus. The applied anatomy and physiology of the upper oesophageal sphincter are first described. The chapter then details the management of cricopharyngeal dysphagia, with and without a pharyngeal pouch. Management of the conditions requires consideration of medical, endoscopic and open surgical approaches. All of these are discussed.

DEFINITION

The terms cricopharyngeus and upper oesophageal sphincter are often used interchangeably. The cricopharyngeus is the most inferior part of the constrictors of pharynx. The upper oesophageal sphincter is the term used to describe the area of the digestive tract at the junction of the pharynx and oesophagus. This term perhaps oversimplifies the functional zone of the lower pharynx and upper oesophagus. Rather than being a simple sphincter made up of a circular muscle lying at the lower border of the pharynx, the functional area is most likely an inverted cone shape with the cricopharyngeus at the lower end of the confluence of the piriform fossae and indented anteriorly by the cricoid cartilage. Opening and closing is a complex function influenced by this circular muscle as well as the position of the cricoid cartilage in relation to the lumen of the upper oesophagus.

Cricopharyngeal dysphagia is difficulty swallowing due to dysfunction of the cricopharyngeal muscle. Dysfunction is failed relaxation due to fibrosis or muscle spasm. This can occur either with or without the formation of a pharyngeal pouch.

A pharyngeal pouch is a herniation of pharyngeal mucosa through a defect (usually posterior) in the pharyngeal wall. The terms Zenker's diverticulum and hypopharyngeal diverticulum are also used.

The most frequent location of the herniation is the posterior wall of the pharynx through an area of natural weakness between the two parts of the inferior constrictor muscle. This area was described by Killian in 1908 and is referred to as Killian's dehiscence.[1]

INCIDENCE

It is difficult to quantify the incidence of pharyngeal pouch in the general population because not all patients present to a specialist. The incidence of presentation to an ear, nose and throat (ENT) specialist has been estimated as

0.47–1 cases per 100 000 per year.[2,3] Pharyngeal pouch is more common in men, with a ratio of approximately 2 : 1. Patients are usually over the age of 50 years with the most common presentation being between the sixth and ninth decades. In an ageing population, it might be expected that prevalence will increase. The condition of pharyngeal pouch affects Caucasians and is rare in Asian and Afro-Caribbean races.

DIAGNOSIS

Patients present with symptoms of variable severity, not necessarily related to the size of the pouch. Most patients present with long-standing symptoms; indeed, it is the insidious onset and slow progression of the symptoms that cause many patients to present with a well-developed pouch and sometimes severe weight loss.

Dysphagia is the most common symptom and is present in virtually all patients. Dysphagia means that the patient must have either a mechanical blockage or neuromuscular incoordination or both. Dysphagia should be distinguished from the sensation of a lump in the throat that typifies the globus syndrome. In a patient with a pharyngeal pouch the early symptoms are of solids sticking in the throat with the need to swallow several times to clear the food. Frequently, the patient attempts to chew every mouthful of food down to small fragments. As the condition progresses, it becomes impossible to enjoy a meal with friends, owing to the excessive length of time taken to eat the meal and the fact that regurgitation sometimes occurs. Eventually, dysphagia with semi-solid foods and then liquids develops. Occasionally, patients present with total dysphagia, unable to swallow their own saliva. Severe weight loss and malnutrition accompany this final state. Painful swallowing in very unusual and should raise suspicion of a malignancy.

Regurgitation of undigested food is a very common presenting symptom. Undigested food may regurgitate into the mouth during a meal, although more often it is after the meal. The regurgitation is more likely to happen when the patient is lying down, and sleep may be disturbed by it. A few patients solve this problem by evacuating the pouch before going to bed by pressing on the side of their neck. Frequently, there is stasis of food in the pouch and this leads to a 'foul taste' and friends or relatives may complain about the patient's halitosis.

Pulmonary complications may arise and result from aspiration of the pouch contents into the larynx. The patient may complain of a persistent cough or throat irritation. The aspiration may lead to chest infections, pneumonitis, lung abscess, bronchiectasis and lung collapse. Hoarseness occurs due to laryngitis caused either by aspiration or gastric reflux, which commonly coexist. The voice might also have a 'wet' quality due to stasis of fluid and soiling of the larynx.

The patient may complain of a lump in the neck that appears intermittently, and gurgling noises in the neck are sometimes noticed (cervical borborygmi). The patient is often aware that food is sticking in the upper throat and frequently will point to the region just below the cricoid cartilage.

Clinical examination may reveal a thin or malnourished patient. The endoscopic view of the larynx and pharynx may be normal although sometimes 'pooling of saliva' can be seen. Rarely, a soft compressible swelling may be found in the neck, usually on the left side in the anterior triangle. The 'rising tide' clinical sign has been described in this setting. During flexible endoscopic evaluation of swallowing using fluids (usually with water or milk with dye), small amounts of swallowed fluid can be seen to rise up from the postcricoid region after the bolus has disappeared from view.

The differential diagnosis includes all motility disorders of the pharynx and oesophagus (globus, scleroderma, achalasia) as well as structural oesophageal disease (neoplasm and strictures) and, finally, neuropathies and myopathies. Gastro-oesophageal reflux disease (GORD) is often present and virtually all motility disorders have been reported in association with GORD. The successful treatment of GORD usually improves the symptomatology of all motility disorders, and is certainly relevant in the treatment of patients with a pharyngeal pouch.

The investigation needed to confirm the diagnosis is either a barium swallow or a contrast video swallow (**Figure 52.1**). The latter provides considerably more

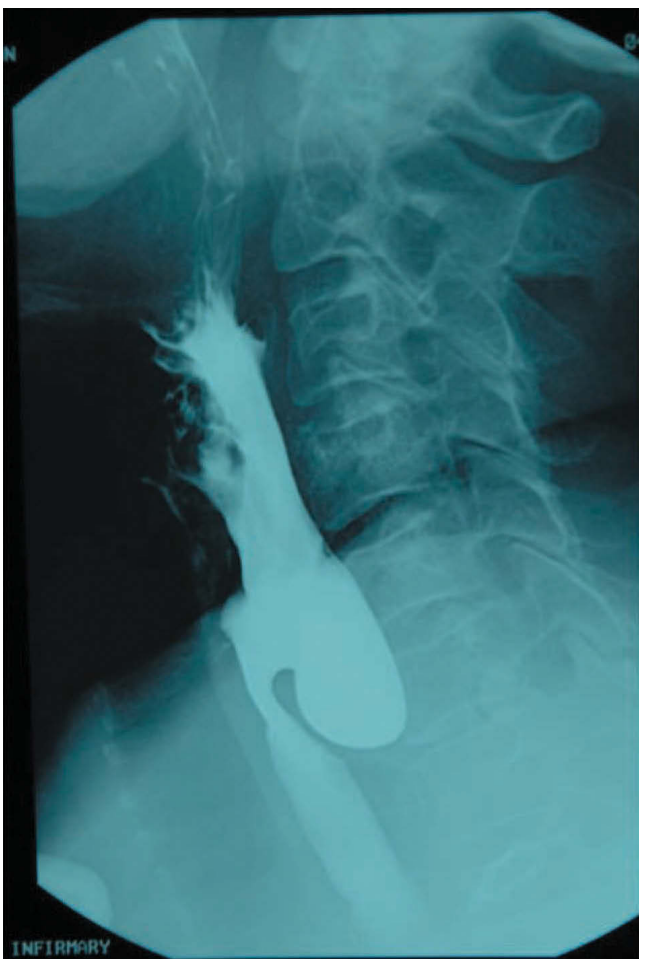

Figure 52.1 Barium swallow showing a pharyngeal pouch.

information about the function of the pharyngeal muscles as well as the presence or absence of gastric reflux.[3] It is essential that the contrast study includes the lower oesophagus and stomach because a lower oesophageal carcinoma can coexist with a pharyngeal pouch.

KEY POINTS

- Incidence is one per 100 000 per annum.
- The condition occurs almost exclusively in Caucasians.
- Dysphagia, regurgitation, hoarseness and pulmonary complications are the main symptoms.
- Differential diagnosis: globus, scleroderma, achalasia, neoplasm, stricture, neuropathies.
- There is a common association with gastro-oesophageal reflux.
- Contrast study is required and a dynamic video swallow is best.

AETIOLOGY

Over the years, many theories concerning the aetiology of pharyngeal pouch have been advanced but no one theory is accepted. There is agreement about the site at which a pouch forms: the posterior wall of the most caudal part of the hypopharynx between the oblique fibres of the thyropharyngeus muscle and the horizontal fibres of the cricopharyngeus muscle. The area between these two muscles is triangular and there are very few muscle fibres in this part of the pharyngeal wall (**Figure 52.2**). This triangular area is called Killian's dehiscence after the man who first described it in 1908. With the advent of more sophisticated and accurate manometric methods for measuring pharyngo-oesophageal sphincter function, one might have hoped for a common consensus on aetiology. On the contrary: even the most popular theories continue to be questioned.

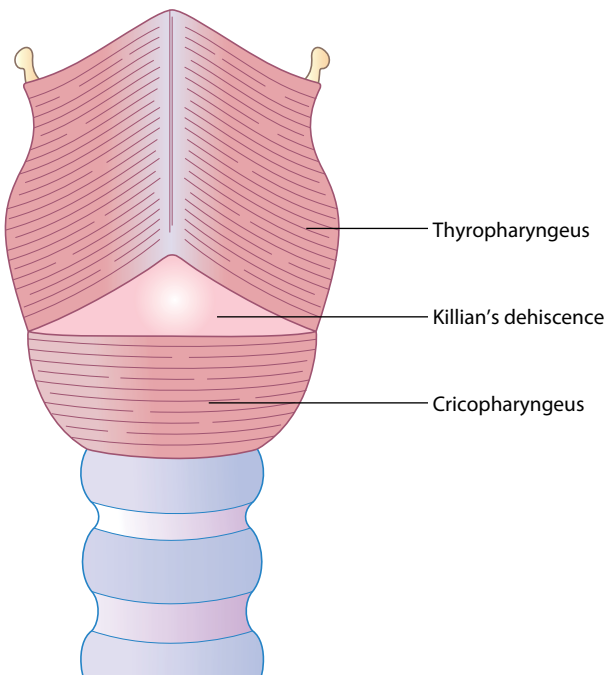

Figure 52.2 Killian's dehiscence.

The three main theories currently proposed to explain the formation of a pouch are:

- that it occurs mainly because of an anatomical weakness in the pharyngeal wall
- spasm of the cricopharyngeus muscle
- various theories that can be labelled as incoordination of the pharyngeal muscles.

Killian's dehiscence; an area of anatomical weakness

Van Overbeek has proposed that anatomical dehiscence is the major cause of pharyngeal pouches.[4] He reasons that, in humans, the larynx is an important structure generally larger than in other animals. In most mammals, the larynx is located just below the skull base, but in humans it has descended to the cervical region. Consequently, the pharyngeal constrictor muscle fibres in humans (with the exception of cricopharyngeus) have assumed an oblique course because the raphe in the dorsal midline is attached to the skull base. However, the cricopharyngeus muscle has horizontal muscle fibres which arise from either side of the cricoid cartilage and not the skull base. Therefore, the 'descent of the human larynx' gives rise to Killian's dehiscence. (It should be noted that pharyngeal pouches do occur in other animals.)

Van Overbeek further proposes that individual variations in anatomy are the cause of a predisposition for hypopharyngeal diverticulum; for instance, some individuals with longer necks might have a larger triangle of Killian.[4] Perrott studied the pharyngeal muscles in cadavers and found several different patterns of fibre arrangement in the gap between thyropharyngeus and cricopharyngeus, and in each individual muscle.[5] He suggested that in some individuals the arrangement of the cricopharyngeus muscle leaves denuded portions, and therefore these individuals were more liable to pouch formation.

To account for the fact that pharyngeal pouches develop after 40 years of age, Van Overbeek suggests that, with advancing age, there is loss of tissue elasticity and a decrease in muscle tone. The large size of the laryngeal skeleton may explain why pharyngeal pouches are more common in men.

That an anatomical predisposition may play a prominent role in pouch formation is also supported by the familial incidence seen with these relatively rare diverticula. In Van Overbeek's series of 545 patients with pharyngeal pouch, nine patients were from four families and three of the nine were brothers from the same family. All 545 patients were Caucasian.[4]

Van Overbeek's manometric studies showed that, in normal people as well as patients with a pouch, there is a high intraluminal pressure in the caudal hypopharynx that peaks during pharyngeal contraction. He proposes that, in individuals with an anatomical predisposition (large or weak Killian's dehiscence), a mucosal prolapse takes place

and over the years the intraluminal pressure produces a pulsion diverticulum that gradually increases in size. He found no significant differences in the maximal contraction pressure in the hypopharynx between patients with a pouch and normal individuals, and thus concluded that the problem is due to an anatomical weakness (Killian's dehiscence).

Failed relaxation of the cricopharyngeus muscle

The cricopharyngeus muscle normally is in a state of tonic contraction, but it relaxes at the end of the second stage of swallowing when the sequential contraction of the pharyngeal constrictors occurs from above downwards. Various functional abnormalities have been suggested to account for pouch formation.

Negus,[6] Sutherland[7] and Belsey[8] favoured the theory that persistent tonic spasm of the cricopharyngeus muscle prevents the downward passage of the bolus and creates a high pressure above the cricopharyngeus that eventually causes herniation through Killian's dehiscence.

Dohlman and Mattson[9] stressed the importance of an intact prevertebral fascial layer that normally supports the posterior wall of the larynx. They reasoned that, with increasing age, the fascia may weaken, allowing the larynx to fall forwards and thus decrease the circumference of the cricopharyngeus muscle, which is normally stretched open during the act of swallowing. A functional obstruction would be produced and, with elevation of intrapharyngeal pressure on swallowing, herniation of mucosa through the weakened posterior triangle, now unsupported by prevertebral fascia, would take place.

Cook[10] has more recently proposed that, rather than spasm of the muscle, the failure to relax is due to fibrosis. Laryngopharyngeal reflux is suggested as one possible cause of this.

Some patients with primary muscle disorders such as inclusion body myositis can have failed cricopharygeal relaxation, initially due to muscle failure and laterally due to fibrosis in the muscle. A pharyngeal pouch may then develop above the disease cricopharyngeal muscle.

Incoordination theories

Ardran, Kemp and Lund[11] used contrast cineradiography to examine 16 patients with pouches of differing sizes and 17 normal subjects. After the initial swallow, the main bolus descended into the pharynx to be moved on by the pharyngeal stripping wave. In patients with pouches they found this to be defective in two ways: the oropharyngeal contraction was weak, and the pharyngeal peristaltic wave was also weak together with early closure of the cricopharyngeus muscle. As a result of their studies they proposed a mechanism of pouch formation. The cricopharyngeus contracts prematurely and, as the stripping wave descends to the prematurely closed sphincter, it pushes the posterior pharyngeal wall down and forwards to meet the back of the cricopharyngeal sphincter. A dimple is produced which, in time, goes on to form a pouch.

Ellis et al[12] came to similar conclusions by measuring the intraluminal pressures in patients with pouches and comparing them with those of normal subjects. The resting tone of the cricopharyngeus was found to be normal in all subjects, but in patients with a pouch the cricopharyngeus was found to contract a fraction of a second before pharyngeal contraction was complete so that the pharyngeal–oesophageal peristaltic sequence was not coordinated.

Lichter et al[13] also supported the incoordination theory. His manometric study showed that, although the sphincter relaxes for the normal amount of time, relaxation begins prematurely and therefore ends prematurely. The effect is the same: high pharyngeal pressures conducive to herniation of mucosa through a muscle-deficient area. Lichter also noted the phenomenon of repetitive pharyngeal swallow, thought to be a result of obstruction to the swallow wave at the upper oesophageal sphincter, since it disappeared following sphincterotomy.

Hunt[14] proposed that gastro-oesophageal reflux may lead to cricopharyngeal spasm or incoordination. The reported incidence of gastric reflux in patients with pharyngeal pouches ranges from 5% to 100%, with the incidence in the normal population being put at 23%.[15] The wide variation in these series could easily be explained by how persistently the symptom of reflux was sought and interpreted. Resouly et al[16] studied 29 patients who underwent surgical correction of pharyngeal pouches. Of these, 19 were found to have reflux and 20 dysmotility. Their findings suggest that many patients with a pouch may have a generalized oesophageal muscle dysfunction and not purely a localized incoordination of the cricopharyngeal muscle.

Rarely, a pharyngeal pouch may form by traction as opposed to pulsion. The adhesions associated with surgery to fuse the anterior cervical spine following trauma can 'pull' a pouch out of the pharynx.[17, 18]

Similarly, pouches (or more correctly pseudopouches) may appear in the presence of large anterior cervical spinal osteophytes over which the pharynx moves, causing an apparent pouch. When examined, such sacs do not herniate through muscle and disappear on removal of the osteophytes.[19, 20]

In summary, opinion concerning the pathophysiology of pharyngeal pouches is divergent. Part of the disagreement may be ascribed to differences in measuring techniques.

CONCLUSION

It is unlikely that there is a single pathophysiological process causing pharyngeal pouch formation. However, in general terms, incoordination between the descending peristaltic wave and failed cricopharyngeal muscle relaxation creating an abnormally high intraluminal pressure subsequently leads to mucosal herniation through the weak area of Killian's dehiscence.

As most agree that failed cricopharyngeal muscle relaxation is involved in the aetiology of pouch formation, a cricopharyngeal myotomy is recommended. With endoscopic techniques this is always carried out because the

cricopharyngeus muscle lies within the bar that divides the pouch from the oesophagus. For operations involving pouch excision, a separate myotomy is required.

KEY POINTS

- Killian's dehiscence is an area of potential weakness between the thyropharyngeus and cricopharyngeus muscle.
- Dysfunction of the cricopharyngeus muscle (or failed cricopharyngeal relaxation) is involved in pouch formation.
- Gastro-oesophageal reflux may contribute.

PATHOLOGY

The histology of an excised pouch shows an epithelial lining of stratified squamous epithelium and submucosa, often surrounded by fibrous tissue. Nearer the neck of the pouch, scanty muscle fibres are found in the wall.

There is evidence of myositis either isolated or as part of a systemic disease (e.g. inclusion body myositis) in some patients.

Carcinoma occurring within a pouch

Carcinoma within a pouch was first described by Vinson in 1927; it is a rare problem with only 47 cases reported in the English literature.[21] Huang et al,[22] in a series of 1249 patients, found four patients with a malignancy arising within the pouch, an incidence of 0.32%. In Van Overbeek's series of 545 patients only two (0.4%) had a carcinoma.[4] However, Bradley et al, in a retrospective review, found that out of 50 pharyngeal pouch excisions, two had carcinoma *in situ* and two had invasive carcinoma.[23]

Carcinoma usually seems to occur in individuals who have had a very long-standing pouch, with the average duration of symptoms in Huang et al's four patients being greater than 7 years. The main predisposing factor is thought to be chronic irritation and inflammation of the pouch lining caused by food retention.

It has been stated that barium studies show a constant filling defect as opposed to the filling defect due to food debris, which may move or alter between films. Symptoms indicating a carcinoma are rapidly increasing dysphagia, pain and/or blood in the regurgitated food. Nodes or a mass in the neck may be found. Patients with a pouch do not normally complain of pain or bleeding and the dysphagia usually progresses slowly. An urgent endoscopy is required in any individual with these suspicious symptoms, whether or not they have had a pouch treated before.

The endoscopic management of a pharyngeal pouch should include a close inspection of the pouch lining with a biopsy of any areas that look suspicious. Close inspection with a Hopkins rod is recommended and it may be necessary to wash the food debris out of the pouch with saline in order to obtain a reliable view of the pouch mucosa.

Carcinoma arising after pouch surgery

At a meeting in 1951, Lodge was the first to question the possibility of a carcinoma arising in the pouch wall following Dohlman's procedure. To this Professor Dohlman replied: 'I suppose the operation, as soon as it relieves the retention in the sac, contributes to a more normal appearance and function in the mucous membrane, and consequently diminishes the danger of cancer.'[24] However, carcinoma certainly can arise in the pouch wall following endoscopic division of the cricopharyngeal bar and after pouch excision (at the junction of pouch and oesophagus). In all reported cases there has been a delay of several years before the carcinoma occurred and often the patient has had persistent symptoms and multiple procedures.[25]

KEY POINTS

- Carcinoma developing in a pouch is rare (0.4%).
- At operation, it is essential to examine the lining of the pouch.
- Carcinoma can rarely occur after pouch surgery.
- Rapid-onset dysphagia, pain or blood-stained secretions should raise suspicion for malignancy.

MANAGEMENT OPTIONS

The management options for patients with a pharyngeal pouch can be divided into three groups: conservative, endoscopic surgery and external approach surgery. Particularly for patients with a pharyngeal pouch, it is essential to consider the overall health of the patient carefully as well as assessing how much effect the pouch is having on the individual's quality of life. A small pouch may cause minimal symptoms, in which case the patient may or may not present to their general practitioner.

Careful consideration of the patient's general health and their specific symptoms needs to be undertaken. When weighing up the decision as to whether to operate or not it is important to consider that the symptoms associated with a pharyngeal pouch usually increase with time whereas the elderly patient's overall health tends to decline. In Zenker's original review, 13 of 22 patients died because of the complications associated with living with a pouch.

The majority of patients undergoing pharyngeal pouch surgery are elderly and frail. The mortality rates observed in some of the published series are a reflection of this frailty. Therefore, the ideal surgical method is one that requires a short anaesthetic and the minimum surgical intervention. The modern endoscopic technique employing stapling fulfils these criteria.

Pouch operations include:

- endoscopic:
  - fibre-optic (flexible) endoscopy and division of cricopharyngeus (diathermy)
  - rigid endoscopy and diathermy division of the cricopharyngeal bar

  - rigid endoscopy and laser division of the cricopharyngeal bar
  - rigid endoscopy and division of the cricopharyngeal bar by a cutting and stapling device
- open cricopharyngeal myotomy
- open excision of the pouch with/without cricopharyngeal myotomy
- inversion of the pouch and cricopharyngeal myotomy.

HISTORICAL COMMENT

Ludlow of Bristol was the first, in 1769, to identify a patient with a pharyngeal pouch.[26] In 1878 the clinical features were reported by Zenker,[27] who described a hypopharyngeal diverticulum as a pulsion diverticulum above the oesophageal inlet.[27]

In 1886, Wheeler[28] reported the first successful excision of a pharyngeal pouch, performed the year before, in 1885. It was an incidental finding while operating on an army officer who had acquired a lateral pharyngocoele from overexercising his voice on the parade ground. This patient recovered completely and his swallowing returned to normal. However, many of the early attempts at excision were unsuccessful, being complicated by sepsis and, in particular, mediastinitis. Other methods were therefore advocated including inversion of the sac and diverticulopexy, in which the fundus of the sac is secured high up in the neck. All types of pharyngeal pouch surgery had high mortality rates until the advent of antibiotics; Stetten,[29] in 1910, reported a 17% mortality rate for pouch excision.[29] Even when antibiotics were available, external excision of a pharyngeal pouch continued to carry significant morbidity and mortality. A high fistula rate meant that in most series of pouch excision the average length of hospital stay was in excess of 12 days.[30] The use of an autosuture stapling device to excise the pouch, while at the same time sealing the wound edges, improved the results for pouch excision considerably.[31, 32]

Inversion of a pharyngeal pouch was first described by Girard in 1895.[33] This technique was developed to avoid the risk of opening the sac, associated as it was with the serious problems of sepsis and fistula formation. Stell repopularized this technique, which, when compared with pouch excision, has a lower complication rate and the patient has a shorter hospital stay.[34, 35]

The principle of endoscopic treatment, in which the cricopharyngeal bar is divided to create a common cavity so that the bolus must pass into the oesophagus, was first described by Mosher in 1917.[36] The common wall between the oesophageal lumen and the pouch was divided with punch forceps. Mosher noted that 'a small cresenteric rim was to be left at the bottom of the pouch to wall off the mediastinum' and that 'should symptoms return, it should be an easy matter to cut the common wall still more'. Six patients were treated successfully until Mosher discontinued the procedure when his seventh patient developed mediastinitis and died.

The concept of creating a common cavity endoscopically was restored to favour by Dohlman and Mattson.[9] Dohlman introduced diathermy for coagulating the common wall prior to cutting it. He pointed out that division of the bar or septum, within which lay the cricopharyngeal muscle fibres, simultaneously produced a cricopharyngeal myotomy. Dohlman carried out 100 diathermy divisions in 39 patients, with no complications and a recurrence rate of 7%. It should be noted that many of his operations involved at least two stages. Other individuals could not achieve his results and this endoscopic procedure using diathermy did not gain universal acceptance because many patients complained of persistent dysphagia after the operation and required revision procedures.[37]

Most retrospective reviews showed that the results for pouch excision and endoscopic cricopharyngeal bar division were similar, with both groups having significant morbidity and a high recurrence rate. However, one individual surgeon's figures did stand out; Van Overbeek's series of patients, all treated endoscopically, is still the largest. The first 328 patients were treated by Dohlman's procedure using diathermy and, subsequently, 216 patients were treated with a microscope coupled with a carbon dioxide laser to divide the bar. Van Overbeek's success rate surpassed all other published series at the time and had the lowest complication rate.

In the early 1990s, developments in laparoscopic surgery produced stapling devices that allowed division and sealing of tissue simultaneously.[38] Collard was the first surgeon to use a cutting stapler to divide the common wall between the pouch and the oesophagus while at the same time sealing the opposing walls of the pouch and the oesophagus.[39] Independently, in 1993, Martin-Hirsch and Newbegin published a case report describing a similar endoscopic technique using a stapling gun.[40] Several centres then developed and refined the technique, so that by the time of a 1996 survey 28% of ENT surgeons in the UK were using a stapling device if they used an endoscopic technique. In the following year, the National Confidential Enquiry into Perioperative Deaths (NCEPOD) in the UK recommended that endoscopic stapling should become the treatment of choice.[41] This enquiry also recommended that there should be one or, at the most, two surgeons within each ENT department who are trained and competent in the surgery of pharyngeal pouches. Following this recommendation there has been a shift away from pouch excision.

Cricopharyngeal myotomy via an external incision still has a role, in particular for patients with a very small but symptomatic pouch.

The indications for excision include the presence of a carcinoma in a pouch and a large perforation if it happens during attempted endoscopic stapling.

Table 52.1 describe the authors' approach to surgery for symptomatic pharyngeal pouches.

CONSERVATIVE MANAGEMENT

There is no evidence that any drug therapies work for cricopharyngeal dysphagia.

Botulinum toxin has been injected both percutaneously and endoscopically. Success is variable, and there

TABLE 52.1 The authors' approach to surgery for symptomatic pharyngeal pouches

Size of pouch	First-line treatment	Recurrence/failure/poor access
Small (less than 2 cm)	Balloon dilation of cricopharyngeus *or* Endoscopic division of the cricopharyngeal bar (LASER)	Endoscopic division of the cricopharyngeal bar (LASER) *or* Open cricopharyngeal myotomy
Moderate (2–4 cm)	Endoscopic stapling	Revision stapling *or* Open excision of the pouch and cricopharyngeal myotomy
Large (greater than 4 cm)	Endoscopic stapling *or* Open excision of the pouch and cricopharyngeal myotomy;	Revision stapling *or* Open excision of the pouch and cricopharyngeal myotomy;

are reports of protracted dysphagia due to dysmotility and also of paralysis (temporary) of the larynx.

OPERATIVE DETAILS OF THE METHODS AVAILABLE FOR PHARYNGEAL POUCH SURGERY

Endoscopic stapling technique

In order to obtain informed consent, a thorough discussion with the patient is required. The following points need to be discussed.

- The possibility of not being able to complete the operation safely exists. During the pre-operative assessment it should be possible to identify the patients in whom access may be difficult. The biggest problem encountered is prominent teeth and this may be combined with retrognathia. These patients should be told that it may not be possible to staple the pouch safely, and an alternative strategy should be discussed prior to surgery.
- Patients should be told that there is a risk of damaging their teeth.
- There is a risk of perforating the pouch during attempted endoscopic stapling. Should this happen, a small tear can be sutured endoscopically or managed conservatively but, if it is a large perforation, it would be prudent to open the neck, find the perforation and excise the pouch. It follows that any surgeon undertaking pouch surgery should be competent in head and neck surgery and the patient should be warned pre-operatively that external surgery is a possibility.
- When quoting figures as part of the informed consent, the optimum arrangement is to quote personal figures if this is possible; if it is not, a conservative interpretation of the outcomes given at the end of this chapter could be used.

Technique: endoscopic

This is a modified version of the technique described by Bates.[42]

The procedure is performed under general anaesthesia with endotracheal intubation (preferably with a microlaryngscopy tube to afford more space). If present, the upper teeth are protected with a gum guard or wet swab; the latter allows a little more room for the scope.

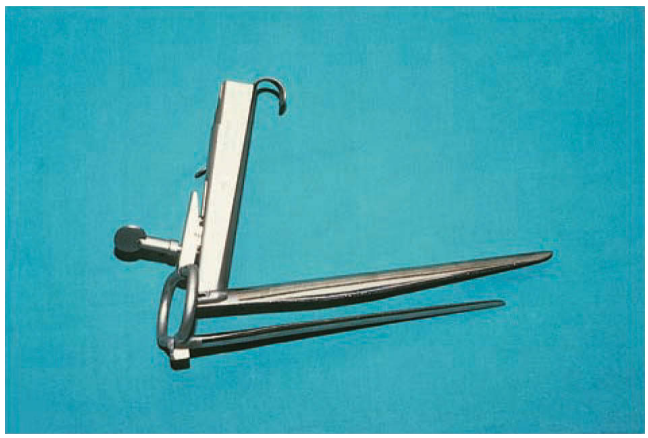

Figure 52.3 A Weerda diverticuloscope.

A rigid Negus pharyngoscope is introduced to identify the cricopharyngeus. At this point any stenosis due to scarring can be dilated with a balloon. A rigid oesophagoscope is then introduced to identify clearly and inspect the upper oesophagus. Then a Weerda distending diverticuloscope (Karl Storz Endoscopy (UK) Ltd, Slough, UK) is introduced (**Figure 52.3**) with confident knowledge of the anatomy of the pouch and any coexisting lesions. (As an alternative, an Oxford Roberts pharyngoscope may be used in a patient with a limited access.) The upper blade of the diverticuloscope is carefully inserted into the oesophagus, with the lower blade simultaneously entering the neck of the pouch. The blades of the diverticuloscope can be adjusted in two directions, and the necessary adjustments are made until a good view of the cricopharyngeal bar is obtained (**Figure 52.4**). The scope is then suspended with a laryngoscope holder. Food debris is gently cleared from the pouch using a sucker and adherent debris can be washed out with saline from a 50 mL syringe.

A Hopkins telescope is used to inspect the lining of the pouch. Any abnormality of the mucosa should be biopsied, although it is rare to have to do this. At times, the lining of the pouch will be inflamed and under these conditions it is important to take extra care, with gentle suction in order

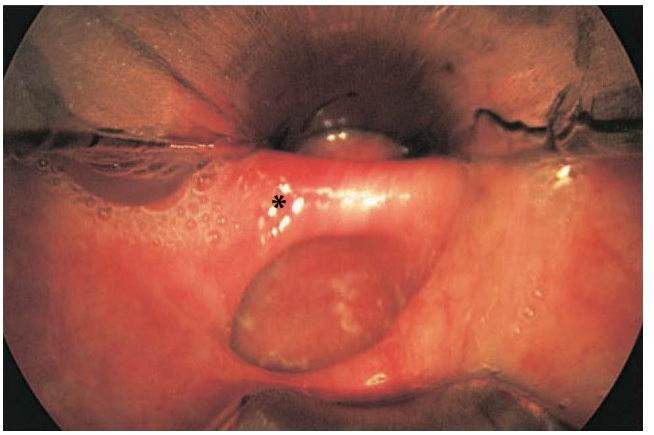

Figure 52.4 The cricopharyngeal bar*.

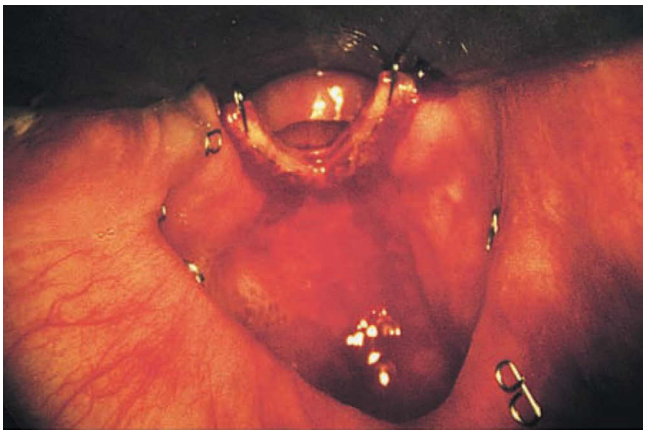

Figure 52.5 A divided and stapled cricopharyngeal bar.

to prevent any bleeding. The presence of blood impedes the view of the operator.

Once a satisfactory view of the cricopharyngeal bar is obtained, an endoscopic linear cutting stapling gun or similar device is removed from the packet and checked. At this stage, the end of the gun carrying the staples is rotated so that the staples are in the upper jaw, which will be inserted into the oesophagus, with the anvil (lower jaw) going into the pouch. Spare staples should be available. The gun is carefully introduced through the Weerda diverticuloscope until the cricopharyngeal bar lies between the two jaws of the gun. The jaws are closed and locked in place. Visual inspection and gentle traction ensure that there is adequate tissue between the jaws. The gun is fired and this divides the septum and simultaneously seals each of the cut edges with a triple staggered row of staples (**Figure 52.5**). The release button is then pressed to free the jaws and the gun is gently removed, making sure that the jaws are not snagged on any tissue.

Tips and tricks for pouch stapling

MAXIMIZING THE VIEW

It is most important to try to obtain the best view possible prior to placing the jaws of the stapling gun over the cricopharyngeal bar. In edentulous patients with a wide mouth, the Weerda scope affords an excellent stereoscopic view and should be used whenever possible. If a good view can be obtained, the operation is usually straightforward. However, difficult access, and a little trauma and possibly bleeding can convert the situation into one where the surgeon will really struggle. A few simple precautions can ensure the best view possible.

- Use a small endotracheal tube or microlaryngoscopy tube, with minimal cuff inflation.
- Ensure that the patient is totally paralyzed.
- Use the Weerda scope if it will fit.
- Use a wet swab to protect the teeth if the access is limited.
- Be prepared to alter the degree of neck extension.
- Use a sucker with great care to limit mucosal damage and bleeding.
- Wash out any debris with 50 mL of saline.
- Use the Hopkins rod.
- Be extremely gentle with the tissues.

DIFFICULT ACCESS

In about 20% of patients access will be difficult owing to a combination of prominent teeth and retrognathia. The anaesthetist will usually confirm that intubation has been difficult (grade 3 or 4). A stiff or arthritic neck needs care but does not often prevent access.

If it is not possible to obtain a view with the Weerda scope, the Oxford Roberts pharyngoscope, the Negus pharyngoscope or the Steiner pattern bivalved laryngopharyngoscope can be used. Each has advantages and disadvantages, but these unfortunately will probably offer poorer visualization than the Weeda diverticuloscope.

NO APPARENT OESOPHAGEAL OPENING

The oesophageal opening is obviously present, but at times it can be hard to find. The reason is that, as a pouch enlarges, the plane of the neck of the pouch rather that the oesophagus comes to lie directly in line with the hypopharynx so that food (and the endoscope) passes into the pouch preferentially. Finding the opening of the pouch is therefore relatively easy, and once found the oesophageal lumen must lie anterior and behind the larynx. The oesophageal opening may appear as a tiny slit or dimple, but when recognized it can be gently dilated using a balloon until the upper beak of the endoscope can be inserted. It can often be found more easily with the use of a Roberts–Jesberg oesophagoscope as this has a slightly upturned superior lip. Also, a fine bougie can be gently passed with its tip bent slightly upwards to cannulate the oesophagus.

DIVISION OF THE SEPTUM

Ideally, virtually all the cricopharyngeal bar should be divided with only a small rim of tissue remaining. Achieving this result is not always easy. The Hopkins telescope can be used to estimate the depth of the

pouch and, with the Weerda scope, it can also be used to check the placement of the jaws of the stapler. It has been suggested to use two endoscopically placed 'stay sutures' to pull the bar up into the jaws of the pouch.[43] It is not possible for the stapling device to cut completely to the end of the cricopharyngeal bar, because the anvil protrudes further than the cutting surface. It is possible to saw the end of the anvil and/or create a deeper pouch by pushing inwards with the jaws, but both these manoeuvres possibly increase the risk of perforation. Leaving an excessively long bar probably predisposes the patient to recurrence but, if in doubt, it is safer to underdivide rather than overdivide the septum and risk a perforation. It is interesting to note that Dohlman was cautious and most of his patients underwent two separate operations. Some surgeons advocate use of the CO_2 laser to divide this last bit of the bar. This does run a higher risk of perforation, as one would expect.

GUN JAMMING

Failure of the stapling gun is rare but the jaws of the gun can jam if too much tissue is placed between them. This occurs when there is a large pouch and the operator is overambitious in trying to do too much with one stapling. In most published series at least two sets of staples are used in the majority of patients. If the gun does jam, gentle manipulation of the release lever will eventually free the mechanism. Do not pull/withdraw a jammed gun; only withdraw when the jaws have been released.

PREVENTING A TEAR/PERFORATION AND SUBSEQUENT MANAGEMENT

It is relatively easy to create a perforation, especially in the pouch itself! The pouch mucosa may be chronically inflamed and, by definition, there is no protective muscle layer. It is possible to push the beak of the scope through the fundus of the pouch or inadvertently tear the pharynx when the stapling device is removed. Occasionally, the stapling device may fail and, if this happens, a diagonal defect in the tissues of the bar appears. Under these circumstances it is possible that the staples have simply not sealed the edges of the tissues properly.

If a small perforation is identified, it may be possible to suture via the endoscope;[44] several endoscopic needle holders are available, such as the 'Berci' needle holder (Stortz). A nasogastric tube should then be inserted and the patient observed carefully for signs of mediastinitis over the next few days.

If a large perforation is present, it is prudent to open the neck, excise the pouch and repair the oesophagus if necessary. Insertion of a large nasogastric tube and a large wound drain is recommended.

If the procedure is traumatic, it is wise to insert a nasogastric tube. In most large series one or more patients are noted to have had a small perforation in the post-operative period because of the presence of surgical emphysema. Conservative management with parenteral feeding and antibiotics is usually successful.

THE LARGE POUCH

Generally, the larger the pouch, the easier it is to deal with using the stapling technique. With a large pouch there is always a long cricopharyngeal bar and as many sets of staples as it takes to divide the bar are used. A huge pouch that extends into the mediastinum is not a contraindication to the stapling procedure, although there is some evidence that large pouches are more likely to recur.[45, 46] Very large pouches may be better treated by open excision; there is no clear evidence favouring either technique, so this has to be carefully discussed with the patient.

THE SMALL POUCH

A patient with a small pouch presents the biggest challenge whether an endoscopic or external approach is used. Unfortunately, small pouches can be symptomatic and some patients who simply have a prominent cricopharyngeal bar and not even a true pouch sometimes also have significant dysphagia. If there is a sufficient cricopharyngeal bar to fill half the jaws of the gun, then stapling is likely to work, but a bar smaller than this makes stapling impossible. Advocates of CO_2 laser division claim that the laser is able to deal with smaller pouches than the stapling device. While this may be true, the margin for error is small. The other options are to let the patient tolerate their symptoms until a more substantial pouch develops, perform an external cricopharyngeal myotomy or simply perform a balloon dilatation of the cricopharyngeus.

PREVIOUS POUCH SURGERY

If the patient has had a previous pouch excision or inversion and then develops a recurrence, it might be assumed that endoscopic stapling would be difficult; this is not the case. Occasionally, scarring twists the pouch to one side but usually the appearances are the same as a pouch presenting for the first time. Following diathermy, laser or stapling division recurrent surgery is usually straightforward.

RECURRENCE

A significant recurrence rate occurs with all endoscopic procedures but, given the minimal discomfort of the first procedure, most patients are usually willing to undergo a repeat stapling, which is not difficult. The same cannot be said for revision external surgery which is difficult and associated with an increased complication rate.

It is arguable whether contrast studies are helpful if a patient has recurrent symptoms after an endoscopic procedure.[47–49] The contrast coats the pouch wall before passing into the oesophagus and the radiologist invariably reports that there is a recurrent pouch. However, multiple pathologies (such as oesophageal dysmotility) can exist, so the authors would recommend a repeat contrast study if surgery is being entertained.

Post-operative care

The patient should not eat or drink for the first few hours after the operation, giving the surgeon time to check the

patient's general well-being and, in particular, confirm the absence of neck or back pain, tachycardia and surgical emphysema. A nasogastric tube is not routinely required but should be inserted if there is significant mucosal damage. Antibiotics are not routinely required and should be reserved for complications. A sensible approach is to allow the patient to drink water initially and then proceed to a soft diet on the evening of surgery if all is well. Many patients can be discharged on the day of surgery.

It is the authors' practice to recommend a soft diet for a week and then progress to a normal diet. The rationale behind this is that the discomfort that can be associated with swallowing can be minimized with a soft diet. Having been denied a good swallow for months, most patients need little encouragement to move on to a normal diet. It seems logical to treat patients with symptomatic gastric reflux with proton pump inhibitors although there is currently no evidence to suggest that this practice reduces the risk of recurrence.

DIVISION OF THE CRICOPHARYNGEAL BAR USING A CO_2 LASER

The Weerda scope is used and the cricopharyngeal bar identified in exactly the same way as for pouch stapling. Swabs soaked in saline are placed around the mouth. An operating microscope with a 400 mm objective lens and attached laser is used. The cricopharyngeal bar is then divided using a CO_2 laser. A nasogastric tube is not essential and the patient is monitored post-operatively in the same manner as for stapling.

Division of the septum using a laser requires experience because it is often difficult to judge the exact amount of septum that can be safely divided without causing a perforation. Inadequate division, on the other hand, results in recurrence of symptoms, requiring revision surgery.

A potential advantage of the laser over the stapling technique is when access is difficult, necessitating the use of a small scope; a better view is obtained because there is no stapling device in the way. The laser can also be used on a cricopharyngeal bar that is simply too small for the jaws of the stapler; however, division of such a small bar does carry with it an increased risk of perforation.

There has been a report of laser endoscopic myotomy with suture closure of the mucosal defect.[41, 50, 51] Although no high-level evidence exists that this represents a better procedure, with modern instrumentation is appears reasonable to close the mucosal defect routinely.

FIBRE-OPTIC ENDOSCOPIC CRICOPHARYNGEAL BAR DIVISION

Fibre-optic endoscopic cricopharyngeal bar division is a technique that uses monopolar cautery to divide the bar. Although approved by the National Institute for Health and Care Excellence (NICE), there are no comparative trials between this technique and established procedures. There are no long-term results available for its efficacy.

The cricopharyngeal myotomy: sole procedure

The approach through the neck tissues is the same as for pouch excision. The assistant passes an oesophagoscope down to just beyond the level of the cricopharyngeus and then withdraws it slightly and rotates the scope so that the light shines through and highlights the muscle fibres, which are divided with a knife. These fibres often do not look substantial and it is important to divide along a length of at least 4 cm. An alternative method is to use the microscope to identify the fibres although it is still helpful to have a solid object, such as a large nasogastric tube, within the lumen. The authors use a pledget to push the muscle fibres apart such that there is at least a 1 cm gap between them. A nasogastric tube is placed by the surgeon in case of any post-operative problems.

Pouch excision

The operation is performed under general anaesthesia with the patient intubated. A pharyngoscope is passed and the openings to the pouch and the oesophagus are identified. A nasogastric tube is passed down the oesophagus. A large bougie can also be passed down the oesophagus alongside the nasogastric tube and can be helpful in the dissection (see below). Food debris is very gently removed from the pouch. The lining of the pouch is carefully inspected with a Hopkins telescope in order to exclude a carcinoma. The pouch is then packed with ribbon gauze soaked in either proflavin or bismuth iodoform paraffin paste, and the proximal end of the strip of gauze brought out through the mouth. The patient is then finally positioned with a sandbag under the shoulders and the head extended and rotated away from the side of the incision.

Either a horizontal incision (usually left sided, level with the upper border of the cricoid), or a vertical incision (along the anterior border of the left sternomastoid muscle) is made. The authors favour a vertical incision for very large pouches. The deep cervical fascia is incised along the anterior border of the sternomastoid muscle, which is retracted laterally. The anterior belly of the omohyoid muscle is divided. The sternohyoid and sternothyroid are retracted towards the midline. The middle thyroid veins are then ligated and divided and this allows the ipsilateral lobe of the thyroid gland to be turned forwards. The contents of the carotid sheath are retracted laterally while the pharynx and larynx are gently rotated to the right. It is good practice to identify the left recurrent laryngeal nerve. It is in close proximity to the inferior thyroid artery, which may have to be ligated and divided. The recurrent laryngeal nerve enters the larynx just inferior to the cricothyroid joint. The dissection is then carried posteriorly along the anterior aspect of the prevertebral fascia so that the tracheoesophageal groove is identified. The pouch will lie immediately above this and can usually be palpated because of the packing within it. It should also be possible to feel the bougie within the oesophagus. This provides 'a base' on which dissection of the pouch can be carried out and it also helps prevent the excessive excision of oesophageal wall.

Sharp dissection of the connective tissue surrounding the pouch is necessary before forceps (Babcock) can be used to grasp the fundus of the pouch. The anaesthetist is then asked to remove the gauze packing. The pouch is carefully dissected free of the oesophagus and the neck of the pouch is carefully cleaned of muscle fibres at its junction with the pharynx.

The pouch should be completely mobilized so that it can be held at right angles to the long axis of the oesophagus, with its neck dissected down to the point where the mucosal sac protrudes through the muscular defect of the pharynx. Care must be taken not to pull normal mucosa out through the deficiency.

A cricopharyngeal myotomy is completed (see 'The cricopharyngeal myotomy: sole procedure' above), and then a large swab should be placed under the pouch to collect any spillage. The neck of the sac is clamped, the pouch excised and the wound edges sealed, preferably using an autosuture stapling gun. A continuous praline suture can be used to invert the suture line.

Recurrence following pouch excision is not uncommon. Contrast studies may be useful in patients who have recurrent symptoms following pouch excision, although a post-operative contrast study by Zeitoun et al[52] showed a multitude of abnormalities even among those patients who were asymptomatic. Their conclusion was that excision of a pharyngeal pouch does not appear to restore a normal swallow.

OUTCOMES

The result of the majority of published series involving ten or more patients is shown in **Table 52.2**. In some of the series, detailed data were collected at the time of surgery but in many of the publications the collection of data was retrospective and is therefore incomplete.

From the data, pouch excision with or without a cricopharyngeal myotomy is an operation that is usually 90% successful, has a recurrence rate of greater than 10% and is associated with major complications in at least 20% of patients. Lengthy anaesthesia is required and the duration of stay in hospital is usually more than 7 days.

Indications for pouch excision remain, including the patient in whom either the pouch or oesophagus is perforated during an attempted endoscopic procedure or the patient in whom a carcinoma is suspected. Some surgeons also advocate pouch excision for young patients and for those with large pouches.[46] The results are better for pouch excision if a stapling device is used to excise the pouch and seal the edges of the pharynx.[31, 32] Pouch inversion also appears to reduce the complication rate but the number of patients reported in the literature is small.[34, 35]

Endoscopic procedures involving division of the cricopharyngeal bar can be seen to produce good results, in particular when the larger series under the care of one surgeon are considered. Dohlman's figures for the period 1940–1960 remain most impressive, with 39 patients being treated with diathermy, a 90% success rate and no major complications.[9] The majority of Dohlman's patients did, however, require two-staged operations. Similarly, Van Overbeek's diathermy series of 328 patients recorded a success rate of 91.5%, a revision rate of 8% and a relatively small number of major complications.[4] **Table 52.3** shows that, when multiple surgeons, each doing a small number of operations, attempt Dohlman's procedure, the success rate drops to 70% with a revision rate of 19%, and the complication rate rises.

With the advent of the Weerda telescope and the CO_2 laser, Van Overbeek changed to laser division in 1981 and his next 216 consecutive patients showed the same success rate and recurrence rate as diathermy, but there was a reduction in the number of complications. When the results of several large studies using the laser technique are summated, it can be seen that the technique has a success rate of 90% and a recurrence rate of 7%. The complication rate is low but higher than for endoscopic stapling.

The results for endoscopic stapling are impressive, with a success rate of 90%, a revision rate of 12% and a very low complication rate.

Long-term recurrence/failure is possibly greater than with open resection, based on the often short follow-up data in endoscopic stapling papers. However, a big advantage of the endoscopic technique is that, when a recurrence occurs, revision is straightforward.

The criticism that a carcinoma may be missed at the time of endoscopic resection is not borne out by the results. There are no reports of this happening in the literature. Bradley's report[23] of a carcinoma *in situ* being found within the wall of a resected pouch of two patients is of concern, and the advice to inspect the mucosa of the pouch thoroughly with a Hopkins rod at the time of the operation seems entirely appropriate. The reported cases of a carcinoma developing some time after endoscopic resection and, indeed, after pouch excision, underline the fact that, if a patient presents with increasing dysphagia, pain or blood-stained regurgitated fluid, then early investigation is required whether they have had pouch surgery or not.

The NCEPOD enquiry noted that pharyngeal pouch surgery is an uncommon procedure associated with a significant mortality of 1–2%. In the year of the study (1995–1996), there were seven deaths following open surgery and one after endoscopic stapling.[41] The one death that followed endoscopic stapling has been published but the other seven have not. The 1996 survey of pouch surgery in the UK showed that 75% of surgeons were doing less than three operations a year. NCEPOD recommended that, because the majority of patients undergoing pharyngeal pouch surgery are elderly and represent a high risk, specialist head and neck surgeons should perform the surgery and, ideally, there should be one, or at most two, surgeons within an ENT department who are trained and competent in this type of surgery. The summated results from the main published series support this recommendation. NCEPOD further recommended that pouch stapling should be the procedure of choice; the summated results indicate that both stapling and laser division of the cricopharyngeal bar should be the operations of choice at the present time.

TABLE 52.2 Results of all the major published series for pouch surgery involving more than ten patients from 1940 to 2003

No.	Author/ref	Date of surgery	No. of patients	Exclusions	No. abandoned	No. of surgeons	Technique	Success	Recurrence	Complications	Length of service (days)	Follow-up (months: mean, range)
Comparative Studies												
1	Dohlman, Mattsson[9]	1940–1960	100	?	?	1	Dohlman's procedure: staged for large pouches	90%+	7%	No major	?	?
2	Aggerholm, Illum[51]	1989–2001	110				Excision (without myotomy)	100/110 (91%)	18/110 (16%)	Fistula: 7 (6%) Mediostinitis: 2 (2%) RLNP: 10 (9%) Other: 13 (12%) Death: 1 (0.9%) Total: (30%)	Not given	Not given
3	Parker, Hawthorne[25]	1962–1971	24	0		Several	Dohlman's procedure	16/24 (66%)	7%	Neck pain: 1	5–6; 2–8	
			7				Excision – myotomy	3/7 (43%)	4/7 (57%)	RLNP: 1 Pneumonia: 2	9	
4	Todd [30]	1950–1972	9				Excision – myotomy	6/9 (66%)	3/9 (33%)	RLNP: 2 Haematoma: ??? fistula: 2		
			48			18	Excision	42/48 (88%)	6/4	RLNP: 9 (19%) Fistula: 9 (19%) Mediastinitis: 2 (4%) Pneumonia: 5 (10%) Stenosis: 3 (5%) Total: (9%)	~18	
			58				Dohlman's procedure	49/58 (84%)	15/58 (26%)	Fistula: 2 Haemorrhage: 1 Stenosis: 2 Total: (9%)	4	
5	Freeland, Bates[34]	1975–1985	19		0	5	Excision ± myotomy	13/19 (68%)	4/19 (21%)	RLNP: 7 (37%) Fistula: 3 (16%)	16	
			9			3	Inversion ± myotomy	7/9 (77%)	1/9 (11%)			

(Continued)

TABLE 52.2 (CONTINUED) Results of all the major published series for pouch surgery involving more than ten patients from 1940 to 2003

No.	Author/ref	Date of surgery	No. of patients	Exclusions	No. abandoned	No. of surgeons	Technique	Success	Recurrence	Complications	Length of service (days)	Follow-up (months: mean, range)
6	Morton, Bartley[35]	1982–1989	15				Excision	14/15 (93%)	1/15 (7%)	RLNP: 1 (7%) Fistula: 2 (13%) Wound infection: 3 (20%)	9 (5–61)	40
			18				Inversion	18/18 (100%)	Nil	1 death (6%)	3 (1–10)	40
7	Van Overbeek[4]	1964–1982	328			1	Dohlman's procedure: staged for large pouch	91.5%	8%	Perforation: 7 (3.3%) Haemorrhage: 4 (1%) Oes/trach fistula: 1 (0.3%) Stenosis: 8 (2%) Mediastinitis: 3 (1.42%) Death: 1 (0.3%)		
		1981–1992	216			1	CO_2 laser: staged for large pouch	90.6%	16/216 (7.4%)	Perforation: 12 (5.5%) Haemorrhage: 1 (0.4%)		
8	Van Eeden, Lloyd, Tranter[48]		18				ESS	83.3%	1/18 (5.5%)		2.26	Average 10
			19				Various	70.6%	3/19 (17.6%)		4	Average 43
9	Moran, Wilson, Al Muhanna[15]	1967–1984	73	14		?1						
			13			?1	Dohlman's procedure	6/13 (46%)	7	RLNP: 1 (7.5%) Perforation: 5 (38%)		
			36			?1	Excision	26/36 (725)	2/36 (5.5%)	RLNP: 2 (5.5%) Fistula: 4 (11%) Stenosis: 2 (5.5%)		
10	Mirza, Dutt, Minhas, Irving[46]	1989–1999	23			7	Excision	22/23 (96%)	1/23 (4%)	Perforation: 3 (13%) RLNP: 1 (4%) Wound infection: 1 (4%)	8.5 (4–16)	
			20			4	ESS	15/20 (75%)	2/20 (1%)	Perforation: 3 (15%)	3 (1–6)	
			9			2	Dohlman's procedure	7/9 (78%)	1/9 (11%)	Perforation: 1 (11%)	5.8 (3–8)	
			3			1	Inversion	3/5 (60%)		Nil	5 (4–6)	
			3			2	Cricopharyngeal myotomy alone	3/3 (100%)		RNLP: 2 (66%)	6.7 (3–10)	

(Continued)

TABLE 52.2 (CONTINUED) Results of all the major published series for pouch surgery involving more than ten patients from 1940 to 2003

No.	Author/ref	Date of surgery	No. of patients	Exclusions	No. abandoned	No. of surgeons	Technique	Success	Recurrence	Complications	Length of service (days)	Follow-up (months: mean, range)
11	Mackay[54]	1957–1994	42			7	Dohlman's procedure		3/42 (7%)	1 developed carcinoma Mediastinitis: 2 Stenosis: 1 Lung abscess: 1 Perforation: 1 Total: 14%	11+ (5–110)	Not given
			30			13				Fistula: 6 RLNP: 2 Emphysema: 2 Stricture: 1 Glottic oedema: 1 Total: 27%	16+ (5–365)	
			20				Dilatation	Mostly ineffective	High			
laser Studies												
12	Benjamin, Gallager[55]	1987–1992	34	0	2		Laser	30/32 (93.8%)	1/32 (3.1%)	Perforation: 2	4.5	Not given
13	Kresper, Kacker, Remacle[56]	1989–2001	69	Pouch <2 cm and 74 cm	3		Laser	58/67 (86%)	6/69 (8.7%)	Perforation: 3 (4%) Bleeding: 2 (3%) Pneumothorax: 1 (1%)	Not given	Average 4.8 (1–121)
14	Bradwell, Bieger, Strachan, Homer[57]	1085–1993	15				Laser	11/15 (73%)	2/15 (13%)	Perforation: 2 (13%) Bleeding: 1 (6.6%)	4.5+ (2–11)	48–132
15	Nyrop, Svendstrup, Jorgensen[58]	1989–1999	61			3	Laser	53/61 (87%)	6/61 (10%)	Bleeding: 1 (2%) Perforation: 3 (5%) Inflammation: 2 (3%)	3 (2–14)	37 (3–96)
16	Lippert, Benedikt, Heinrich, Werner[59]	1984–1996	70				Laser	66/70 (94%)	3/70 (4%)	Mediastinitis: 1 (1%)	Not given	Not given
ESS (stapling) Studies												
17	Cook, Huang, Richstmeier, Scher [43]	1995–1999	74		6	2	ESS	66/68 (97%)	6/68 (8.8%)	Perforation; 1 Dental: 5	1 (0–4)	9.3 (1.5–25)

(Continued)

TABLE 52.2 (CONTINUED) Results of all the major published series for pouch surgery involving more than ten patients from 1940 to 2003

No.	Author/ref	Date of surgery	No. of patients	Exclusions	No. abandoned	No. of surgeons	Technique	Success	Recurrence	Complications	Length of service (days)	Follow-up (months: mean, range)
18	Jaramillo, McLay, McAteer[47]	1996–2000	32	5	2	1+1 supervised registrar	ESS	13/15 (86%)	2/15 (13%)	Perforation: 1 (3%)	3.17 (2–11)	Results of surgery repoerted on 15 patients to having at least 24/12 follow-up
19	Bates, Steventon[60]	1994–2004	230	0	0	1+ supervised registrar	ESS	197/230 (86%)	41/230 (18%)	Dental: 8 (3%) Perforation: 1 (0.4%)	2.1 (1–6)	60 (3–138)
20	Collard, Otte, Kestens[39]	1992	6	0	0	1	ESS	5/6 (83%)	1/6 (16.6)	Nil	2	2–16
21	Sood, Newbigin[45]	1992–1999	37				ESS	32/37 (86%)	4 (9%)	Perforation: 1 Dental: 3 Death: 1	<2	2–43 (19)
22	Counter, Hilton, Baldwin[61]	1993–1997	28				ESS	16/9 (84%)	6/19 (22%)	Perforation: 3 (11%)	4.1 (1–31)	59 (55–73)
23	Raut, Primrose[62]	1994–1998	25			1	ESS	20/25 (80%)	9/25 (36%)	Perforation: 2 (8%)	3.4	24–60
24	Stoeckli, Schmid[63]	1997–2000	30	0	0	1	ESS	96%	1/30 (4%)	Nil		13.2
25	Thaler, Weber, Goldberg, Weinstein[64]	?–2000	23		7		ESS	14/16 (87%)	2/16 (13%)	Nil		
26	Lüscher, Johansen[65]	1997–1998	23	0	0	Limited	ESS	22/23 (96%)	1/23 (4%)	Perforation: 1 (4%)		12 (4–22)
27	Narne, Cutrone, Bonavina et al[66]	1992–1996	102		4	Limited	ESS	96/98 (98%)	4/102 (4%)	Perforation: 1 (1%)	4	16 (1–45)

TABLE 52.3 Summary of different procedures and outcomes

No. of patients	Method	Success	Revision rate	Complications	Length of stay
278	Excision	255 (91%)	40 (14.3%)	LNP: 35 (12.6%) Fistula: 33 (11.9%) Mediastinitis: 4 (1.4%) Stenosis: 5 (1.8%) Pneumonia: 8 (2.9%) Death: 1 (0.4%) Other: 22 (7.9%)	12+
587	ESS	530 (90%)	63 (12.6%)	Perforation: 14 (2.4%) Dental: 15 (2.6%) Death: 1 (0.2%)	2
463	Laser	417 (90.6%)	34 (7.3%)	Perforation: 17 (3.6%) Bleeding: 4 (0.9%) Mediastinitis: 4 (0.86%) Other: 6 (1.29%)	4
100	Dohlman by Dohlman	90%+	7%	No major	
328	Dohlman by Van Overbeek	91.5%	8%	Perforation: 7 (3.3%) Mediastinitis: 3 (1.42%) Stenosis: 8 (2%) Death: 1 (0.5%) Haemorrhage: 2 (0.52%) Fistula: 1 (0.3%)	
79	Dohlman by multiple surgeons	56/79 (70%)	15/79 (19%)	LNP: 1 (1.26%) Perforation: 6 (7.6%) Mediastinitis: 3 (3.79%) Other: 3 (3.79%)	

CONCLUSIONS

The short-term results with endoscopic procedures are superior to external operations. Endoscopic stapling and laser division are quick and bloodless, are associated with minimal discomfort and avoid the need for a nasogastric tube. Endoscopic techniques permit an early oral intake and early hospital discharge, thus reducing the morbidity and costs traditionally associated with pharyngeal pouch surgery. The long-term recurrence of endoscopic techniques is probably higher than pouch excision. However, revision surgery via the endoscope is relatively easy and successful.

The results for stapling and laser division are similar. Stapling has the theoretical advantage of reducing the risk of perforation and mediastinitis, whereas the laser permits a better view when there is limited access.

Cricopharyngeal myotomy as a sole procedure has a role in the treatment of the very small pouch. There remain some indications for pouch excision. The experience of the surgeon appears to be of the utmost importance. At times, pouch surgery can be difficult and the complications life-threatening. Surgeons who have developed an interest in pouch surgery sufficient to publish large series have the best results.

BEST CLINICAL PRACTICE

- ✓ When operating, strive to obtain a good view.
- ✓ Treat tissues with great respect.
- ✓ Carry out a biopsy for abnormal mucosa.
- ✓ If there is significant trauma, insert a nasogastric tube.
- ✓ For a small perforation, use an endoscopic suture.
- ✓ For a large perforation, open the neck and repair.
- ✓ Post-operative contrast studies are unhelpful.

FUTURE RESEARCH

- ➤ The very small pouch is difficult to treat endoscopically. Changes in the design of the stapling device might help resolve this problem, namely a device that cuts and staples along the whole length of its jaws.
- ➤ Access is difficult in 20% of patients. Improvements in endoscopes and viewing telescopes may reduce the degree of difficulty.

- The recurrence rate for all types of pouch surgery is high and may be related to persistent gastric reflux. Aggressive treatment of the gastro-oesophageal reflux may be appropriate but the evidence is lacking.
- Following all types of pouch surgery, patients are rarely completely asymptomatic and it would be useful to have a method for treating these residual symptoms, which are probably due to an underlying neuromuscular incoordination.
- Randomized controlled trials comparing new techniques with established treatments are justified.
- In the UK, virtually all pharyngeal pouch surgery is now performed by ENT surgeons. Subspecialization is slowly happening and is to be encouraged so that, within each major centre, only ENT surgeons with a special interest in pouch surgery should manage pouch patients.

KEY POINTS

- Cricopharyngeal dysphagia results from the failure of the cricopharyngeal muscle to relax. It can occur with or without the formation of a pharyngeal pouch.
- Pharyngeal pouch occurs in elderly, sometimes frail, patients.
- Incidence is one per 100 000 per year.
- Diagnosis is made with a barium or video swallow.
- Surgery improves quality of life.
- Endoscopic resection with a stapling device or laser is generally considered the first-line treatment for most pouches.
- Recurrence is easily treated with endoscopic techniques.
- Carcinoma is rare but vigilance is required.
- Surgeons with a special interest in pouch surgery should treat all patients.

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CHAPTER 53

OESOPHAGEAL DISEASES

Shajahan Wahed and S. Michael Griffin

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SEARCH STRATEGY

Data in this chapter may be updated by a Medline search using the keywords: gastro-oesophageal reflux disease, Barrett's oesophagus, oesophageal motility, oesophageal achalasia, oesophageal cancer, oesophageal perforation, oesophageal disruption, Boerhaave's, oesophageal foreign body, eosinophilic oesophagitis. The fifth edition of the textbook *Oesophagogastric surgery* was also consulted in preparing this chapter.[1]

INTRODUCTION

A broad spectrum of benign and malignant conditions affects the oesophagus. This chapter concentrates on the main conditions dealt with by upper gastrointestinal surgeons and some gastroenterologists, recognizing that some patients present first to the ENT surgeon depending on the predominant symptoms. Malignant disease and several of the less common benign conditions are managed in specialist oesophagogastric centres in order to improve knowledge, achieve standardization of treatment and, most importantly, improve outcomes.

GASTRO-OESOPHAGEAL REFLUX

Gastro-oesophageal reflux disease (GORD) is extremely common, with symptoms triggered by food, gastric acid or bile from the duodenum travelling back up into the oesophagus.

Presentation

The most common symptoms include retrosternal pain, heartburn, dyspepsia, waterbrash, pain on swallowing, regurgitation and vomiting. Symptoms typically become apparent after meals or when lying supine. A small minority of patients present with atypical symptoms related to proximal reflux. These include voice changes, coughing, sore throat, throat clearing or even sinusitis. Reflux and micro-aspiration might account for worsening of respiratory symptoms in patients with underlying lung disease.

Risk factors include being overweight, smoking, overeating and leaving only a short interval between meals and sleeping. Spicy foods and alcohol are commonly recognized as substances that precipitate symptoms. The underlying mechanisms for developing reflux can include the presence of a sliding hiatus hernia, a reduction in lower oesophageal sphincter pressure, an increase in the number of lower oesophageal sphincter relaxations, abnormal oesophageal peristalsis that fails to clear any refluxate, poor gastric motility and excessive gastric acid production.

Investigation

All patients over 40 with new onset reflux or a change in long-standing reflux symptoms should be referred for urgent flexible endoscopic assessment. This is not only to identify signs of reflux disease but also to exclude malignancy. Endoscopy should be performed while patients are not on any acid-lowering treatment. Appearances might demonstrate oesophagitis, the presence of a sliding hiatus hernia that would predispose to reflux disease, bile reflux or acid-related strictures or they might be normal (**Figure 53.1**).

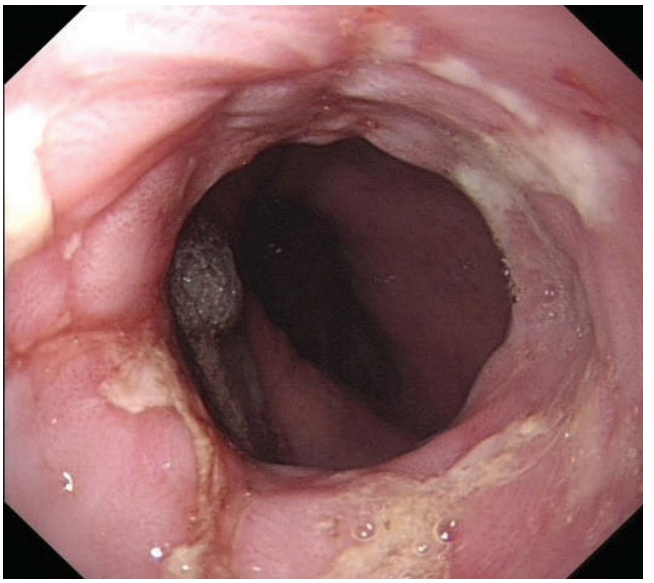

Figure 53.1 Endoscopic view of moderate oesophagitis above a sliding hiatus hernia.

Further investigation is only required in a minority of patients where endoscopic appearances are equivocal in supporting the diagnosis (particularly in cases where non-acid reflux is suspected), if surgery is being contemplated, or in cases of suspected proximal reflux.

Oesophageal manometry assesses the adequacy of peristalsis and can identify any underlying motility disorders. A fine catheter placed in the oesophagus records pressures at rest and during the passage of 10 swallows at various levels along the oesophagus and the oesophagogastric junction. Conventional manometry uses eight channels and displays results as a line graph (**Figure 53.2**). Developments in catheters and software has allowed the introduction of high-resolution manometry, where up to 32 channels can be used to give more detailed information and produces images with contrasting colours to represent differential pressure levels (**Figure 53.3**).

Oesophageal 24-hour ambulatory pH monitoring will reveal whether the oesophagus is exposed to acid content for a pathological length of time (pH<4 for more than 5% of the 24-hour period) and allows for correlation with

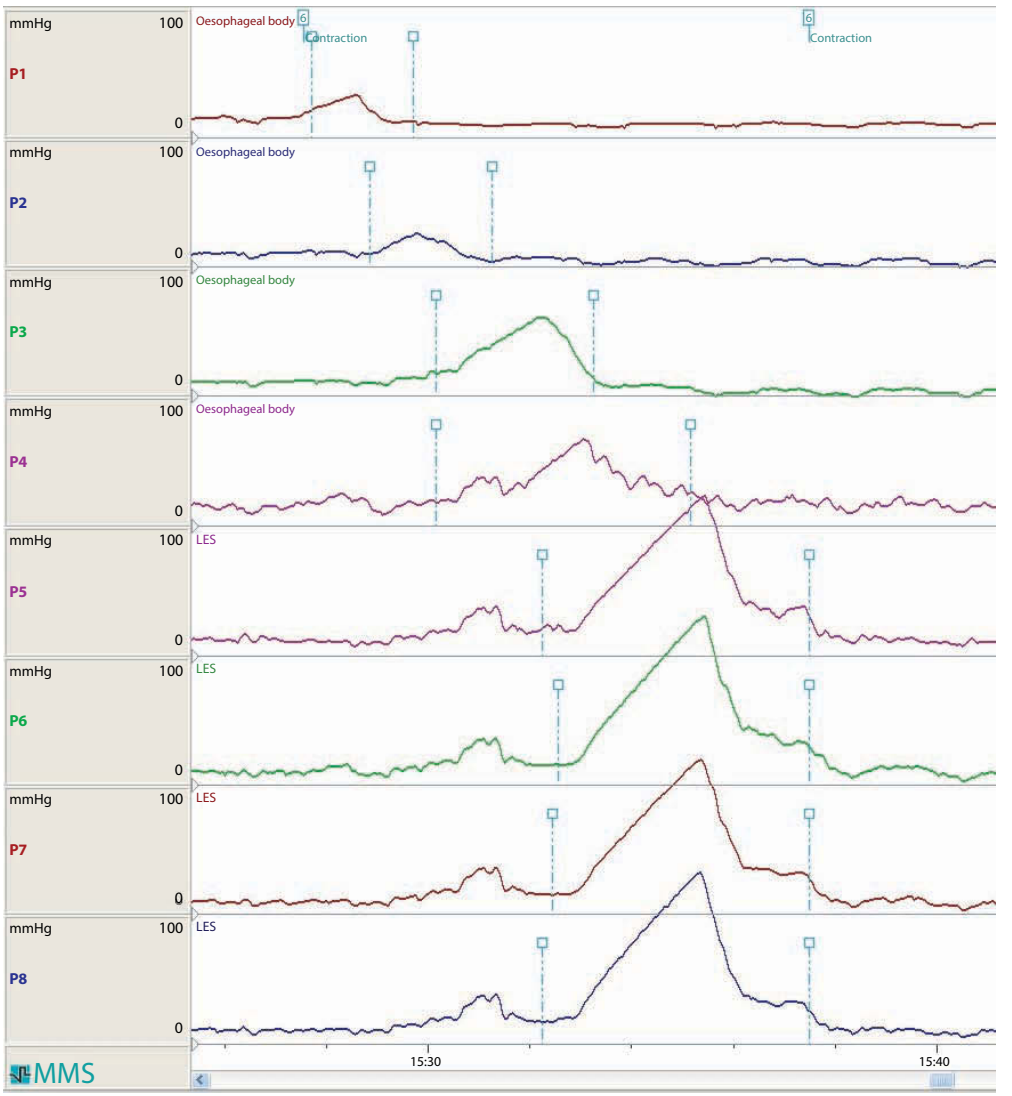

Figure 53.2 Conventional eight-channel manometry demonstrating normal peristalsis within the oesophageal body.

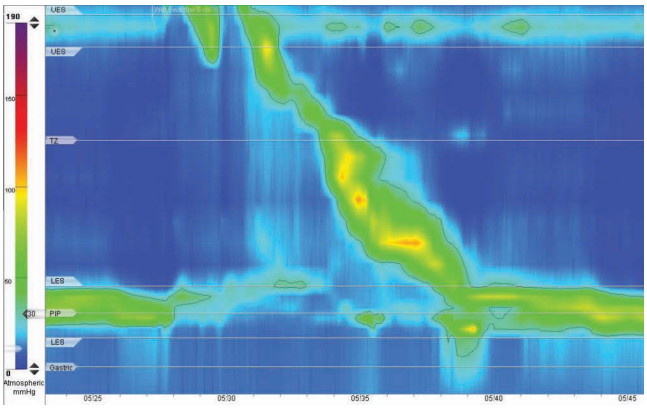

Figure 53.3 Appearances of high-resolution manometry in a normal oesophagus.

any symptoms the patient experiences. Impedance studies are required only in cases of suspected proximal reflux or when non-acid reflux is implicated as the underlying cause. Bile reflux monitoring is possible although is not commonly used. Contrast radiology in the form of a barium swallow can be useful to exclude underlying dysmotility and may also demonstrate reflux.

Management

The overwhelming majority of patients with reflux disease will be managed successfully by addressing risk factors and simple antacids, with proton pump inhibitors required in those with more severe symptoms. The few patients who fail this treatment strategy can be assessed for anti-reflux surgery once the additional investigations have excluded dysmotility and shown evidence of oesophagitis on endoscopy or abnormal acid exposure during 24-hour pH monitoring.[2, 3] Appropriate patient selection is crucial to achieving successful outcomes from antireflux surgery as the potential effects of fundoplication in the wrongly selected patient are disabling.

The standard operation involves a fundoplication where the fundus of the stomach is wrapped around the gastro-oesophageal junction. This is performed laparoscopically in most centres because of reduced post-operative pain and length of hospital stay (often day case) although open surgery perhaps improves the longevity of the fundoplication.[4] A floppy Nissen fundoplication involves a loose, posterior 360-degree wrap combined with tightening of the crura, although variations are practised.[5–8] Whether tailoring of the wrap improves outcomes is not conclusive.[9] Complications from surgery include dysphagia, retrosternal pain, gas bloat, excess flatus and oesophageal perforation. Revisional antireflux surgery is challenging and includes patients with short-term as well as long-term symptom recurrence.[10] Resumption of proton pump inhibitor treatment will suffice in many cases although revisional fundoplication is an option. Subtotal gastrectomy and a roux-en-y reconstruction is reserved as a definitive procedure to relieve intractable symptoms. Newer endoscopic and robotic antireflux techniques remain unproven.[11, 12]

Reflux disease appears to accelerate the development of bronchiolitis obliterans in some lung transplant recipients.[13] This has led to antireflux surgery being considered in such patients.[13] Ongoing research is needed to determine which of these patients are most likely to benefit and to decide upon the optimal timing of such procedures. This mechanism is being extrapolated to patients with other respiratory diseases who do not exhibit symptoms traditionally associated with reflux. In future antireflux surgery might be beneficial in preventing reflux-associated lung damage from microaspiration in this group of patients.

KEY POINTS

- Reflux symptoms are common.
- Upper respiratory tract symptoms are rarely due to reflux.
- Patients over 40 with recent onset reflux symptoms need an endoscopy.
- Most patients with reflux disease are managed with lifestyle modification and proton pump inhibitors.
- Only a minority of patients will require surgery (floppy Nissen fundoplication).

BARRETT'S OESOPHAGUS

Barrett's oesophagus develops when the normal oesophageal lining changes from stratified squamous to columnar epithelium (**Figure 53.4**). It is common in the Western world and has an increasing incidence. It occurs as a result of chronic inflammation secondary to acid, alkaline and bile reflux.[14–16] Genetic factors might also increase an individual's predisposition to this condition and its progression.[17] This metaplastic epithelium increases the risk of developing adenocarcinoma of the oesophagus.[18–20] A formal diagnosis of Barrett's requires the reporting of two separate specimens from a specialist gastrointestinal pathologist. Dysplastic changes within the Barrett's epithelium can occur, subclassified as either low-grade or high-grade. Confirmed low-grade dysplasia increases the risk of progression on to high-grade dysplasia or adenocarcinoma although some will not progress.[21, 22] High-grade dysplasia poses a significant risk of developing adenocarcinoma and, given the subjectivity of biopsies, might indicate that there is adenocarcinoma already present. Patients with a diagnosis of low- or high-grade dysplasia within Barrett's oesophagus should be referred to specialist centres for management.

Surveillance

Enrolment of patients in to an endoscopic surveillance programme improves identification of dysplastic changes before the onset of adenocarcinoma and potentially allows less invasive treatment.[23] Despite the logical advantage of surveillance on an individual basis, definitive evidence of benefit has not yet been produced. A randomized study comparing endoscopic surveillance versus symptomatic presentation designed to determine whether surveillance improves survival in patients with Barrett's oesophagus

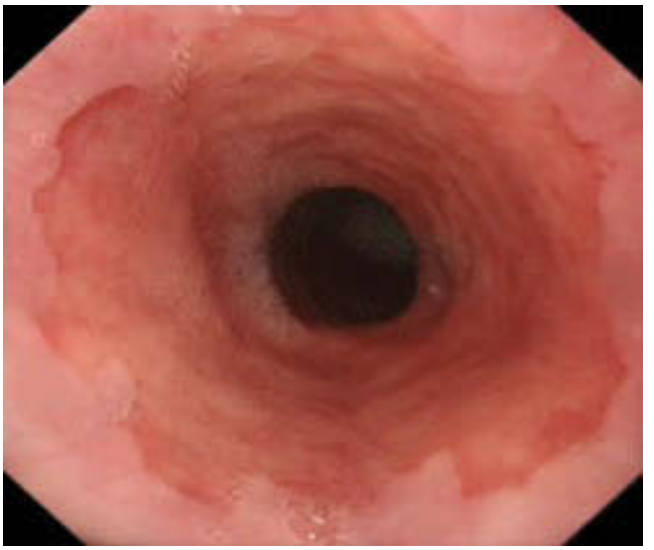

Figure 53.4 Macroscopic appearance of circumferential Barrett's oesophagus.

completed recruitment in 2012. Research using less invasive screening devices that could perhaps identify patients needing endoscopy is ongoing.

Management

The development of Barrett's oesophagus does not require treatment other than addressing risk factors for reflux disease, prescribing proton pump inhibitors to reduce acid reflux and endoscopic surveillance. There is no evidence to suggest that antireflux surgery, which will prevent both acid and alkaline reflux, is superior to medication at preventing progression of the condition.[24, 25]

The development of high-grade dysplasia within Barrett's oesophagus requires full staging to exclude an underlying malignancy with computed tomography (CT), flexible videoendoscopy and endoscopic ultrasound (EUS). Endoscopic mucosal resection (EMR) to obtain a more substantial biopsy might be required (see below). The confirmation of dysplasia will trigger consideration of further treatment.

Radiofrequency ablation

Radiofrequency ablation (RFA) is a newer endoscopic treatment used to destroy dysplastic epithelium.[26] It is indicated in high-grade dysplasia when complete assessment and staging have shown an otherwise normal oesophagus with a flat mucosal lining and an underlying adenocarcinoma has been excluded. It is often used following EMR of a nodular area of Barrett's. Long-term results from this treatment are lacking and there remain concerns about occult neoplasia developing beneath the ablated epithelium.[27] Repeated treatment applications are often required with potential complications of perforation and stricture formation. Intensive endoscopic surveillance is required following treatment to detect any recurrence or new dysplasia that require repeat application or repeat staging. Long-term follow-up of this treatment is awaited and prospective registration of all cases should ensure accurate data.[28] Indications for RFA are likely to expand to include low-grade dysplasia to prevent progression.

Surgery

Oesophagectomy still remains the gold standard for high-grade dysplasia in Barrett's oesophagus as it provides definitive cure. It is indicated when nodal disease is evident on staging suggesting undiagnosed invasive adenocarcinoma, the length of Barrett's oesophagus is extensive or multifocal, the oesophagus is otherwise abnormal or the patient is young. Morbidity and mortality have reduced considerably in oesophagectomy and can be performed with a low mortality and acceptable morbidity. In cases of high-grade dysplasia in Barrett's oesophagus, mortality appears even lower, with one review showing a 1% mortality in 530 patients.[29] More limited resection techniques have also been used.[30]

KEY POINTS

- Barrett's oesophagus increases the risk of developing oesophageal adenocarcinoma.
- Endoscopic surveillance should be offered to patients with Barrett's oesophagus.
- High-grade dysplasia within Barrett's oesophagus indicates the need for full staging and referral to a specialist centre.
- Radiofrequency ablation is a new alternative to surgery to treat high-grade dysplasia in selected cases but long-term results are awaited.
- Oesophagectomy remains the gold-standard treatment for high-grade dysplasia in Barrett's oesophagus.

OESOPHAGEAL CARCINOMA

Incidence

Oesophageal carcinoma is the eighth most common cancer worldwide, with an estimated incidence of 480 000 in 2008.[31] The two predominant types are adenocarcinoma and squamous cell carcinoma. Adenocarcinoma and squamous cell carcinoma differ in several of their risk factors, predominant location within the oesophagus, response to chemotherapy and radiotherapy, and overall survival. Rare cancer types include small cell carcinoma, primary melanoma, malignant stromal tumours and leiomyosarcoma.

The incidence of oesophageal carcinoma increases considerably after the age of 40, with a peak between 70 and 74 years of age for men and a continual rise for females. The cancers have a strong preponderance in affecting males more than females in a 2–4 : 1 ratio.[31]

OESOPHAGEAL ADENOCARCINOMA

This histological subtype predominates in the Western world, accounting for over two-thirds of all oesophageal cancers diagnosed (**Figure 52.5**). The incidence of adenocarcinoma in the Western world is continuing to increase and is the source of concern.[32] These cancers have a

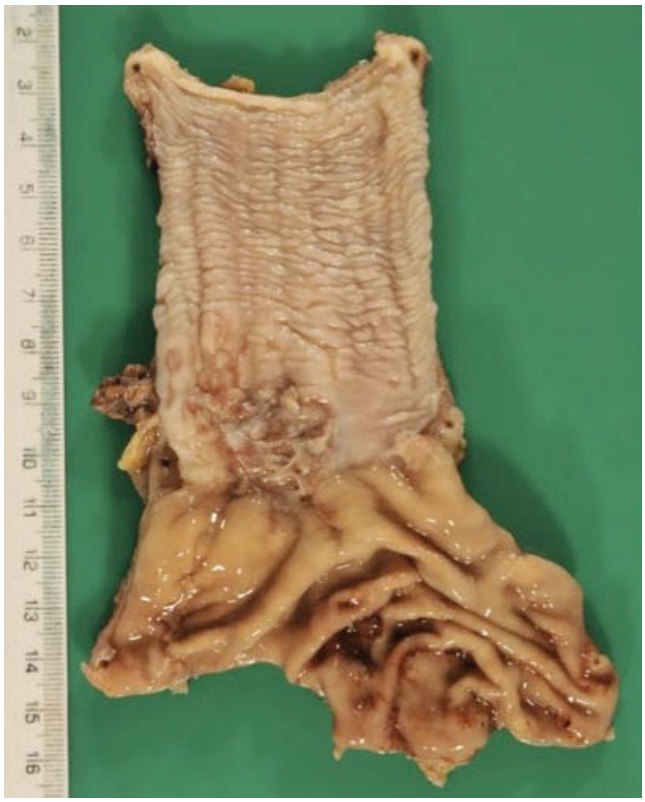

Figure 53.5 Appearance of an oesophageal adenocarcinoma after fixation of the specimen.

tendency to occur in metaplastic columnar epithelium of the middle and lower thirds of the oesophagus or at the oesophagogastric junction. There are concerns that adenocarcinoma might increase in the Far East as Western lifestyles and habits spread.[33] There has also been an increase in the number of oesophagogastric junction adenocarcinomas, seemingly a result of oesophageal cancers migrating distally and gastric cancers migrating proximally over time.

The main risk factors include obesity, reflux disease and the presence of Barrett's oesophagus.[18, 34–36] Smoking, excessive alcohol consumption, a family history of gastrointestinal cancer and diets low in fresh fruit and vegetables are all also implicated in increasing risk of developing oesophageal adenocarcinoma.

OESOPHAGEAL SQUAMOUS CELL CARCINOMA

In contrast squamous cell carcinoma of the oesophagus still predominates in the Far East. These cancers tend to occur in the cervical oesophagus and the upper parts of the thoracic oesophagus. Smoking, high alcohol intake, low socioeconomic status, hot drinks and diets low in fresh fruit and vegetables are strong risk factors in developing squamous cell carcinoma.

Presentation

Presentation often occurs late as many of the early symptoms are non-specific and patients often do not seek medical advice. Attempts at increasing awareness of risk factors and symptoms are important as early disease improves chances of offering curative treatment. Many of the symptoms overlap with benign reflux disease and dysmotility (**Box 53.1**). Early flexible videoendoscopy is essential to capture the patients that have cancer as the underlying cause. Respiratory symptoms can occur due to more proximal reflux and microaspiration from obstruction. Surveillance of patients with Barrett's oesophagus and those with significant family history is designed to identify premalignant changes or early disease.

BOX 53.1 Symptoms suggestive of oesophageal cancer

- New onset or worsening heartburn or reflux in patients aged over 40
- Dysphagia
- Early satiety
- Loss of appetite
- Unexplained weight loss
- Vomiting or haematemesis (less common)
- Voice changes or a persistent cough (less common)

Diagnosis and staging

Diagnosis is made by flexible videoendoscopy, following which patients require fitness assessment, staging investigations and formal discussion at a specialist oesophagogastric multidisciplinary team (MDT) meeting (**Figure 53.6**). These are coordinated through centralized units. This MDT meeting involves oesophageal surgeons, medical and clinical oncologists, radiologists, pathologists, specialist nurses, dieticians, palliative care nurses and a coordinator.

Fitness investigations require a thorough history and examination of the patient, an electrocardiogram, spirometry and a timed exercise test. Formal cardiopulmonary exercise testing (CPET) has been introduced to help objectively measure a patient's fitness in order to quantify risks of treatment.[37, 38] CPET can identify undiagnosed cardiorespiratory comorbidity that might be amenable to treatment before any potential surgery although its precise value is yet to be determined.

Oesophageal cancer and oesophagogastric junction cancers that predominantly involve the oesophagus are staged using the seventh edition of the tumour, node, metastasis (TNM) classification[39, 40] (**Table 53.1**).

Precise identification of the location and depth of the primary cancer, the location and numbers of lymph nodes involved, and the total length of disease taking into account involved lymph nodes will determine available treatment options. Staging investigations as a minimum will include endoscopy, and a gastric protocol CT of the chest, abdomen and pelvis (**Figures 53.7**).

Most patients require additional investigations (**Box 53.2**). EUS is better than CT at identifying local nodes and depth of invasion (**Figure 53.8**). Tumours that demonstrate invasion into the muscular layers of the oesophagus (T3) or involvement of nodes require

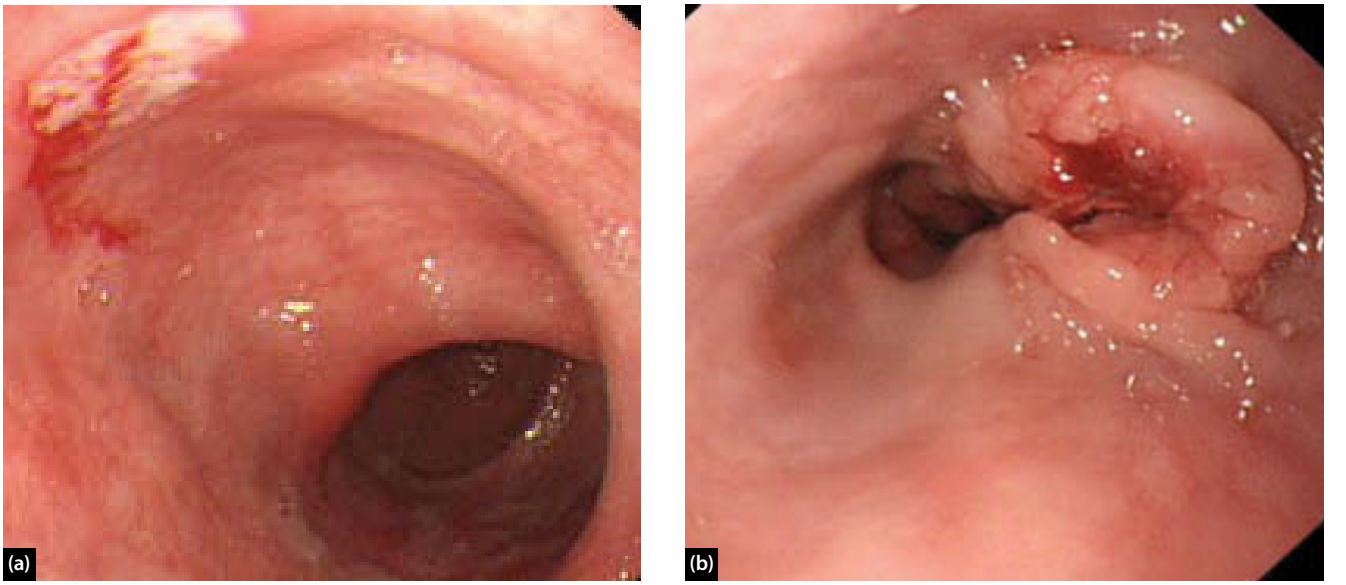

Figure 53.6 The endoscopic appearances of two different oesophageal cancers.

TABLE 53.1 TNM classification of oesophageal cancer

Tis	Carcinoma *in situ* / high-grade dysplasia
T1 T1a T1b	Lamina propria or submucosa Lamina propria or muscularis mucosae Submucosa
T2	Muscularis propria
T3	Adventitia
T4 T4a T4b	Adjacent structures Pleura, pericardium, diaphragm, or adjacent peritoneum Other adjacent structures, e.g. aorta, vertebral body, trachea
N0	No regional lymph node metastasis
N1	1–2 regional lymph nodes
N2	3–6 regional lymph nodes
N3	>6 regional lymph nodes
M0	No distant metastasis
M1	Distant metastasis

additional staging with either bone scan or positron emission tomography (PET-CT) (**Figure 53.9**).

EMR is often required to obtain a more substantial biopsy for small lesions that have inconclusive histology. It may provide a therapeutic option (see below). Neck ultrasound is useful at diagnosing suspicious nodal disease in the neck and can guide fine-needle aspiration cytology. Bronchoscopy and endobronchial ultrasound are occasionally required. Staging laparoscopy is required in patients who have evidence of gastric involvement in locally advanced cancers.

Management

Management is determined by the patient's fitness to undergo radical treatment, the patient's wishes, the stage of the disease and the histological type of cancer.[41, 42] Early cancers include those that are limited to the mucosa,

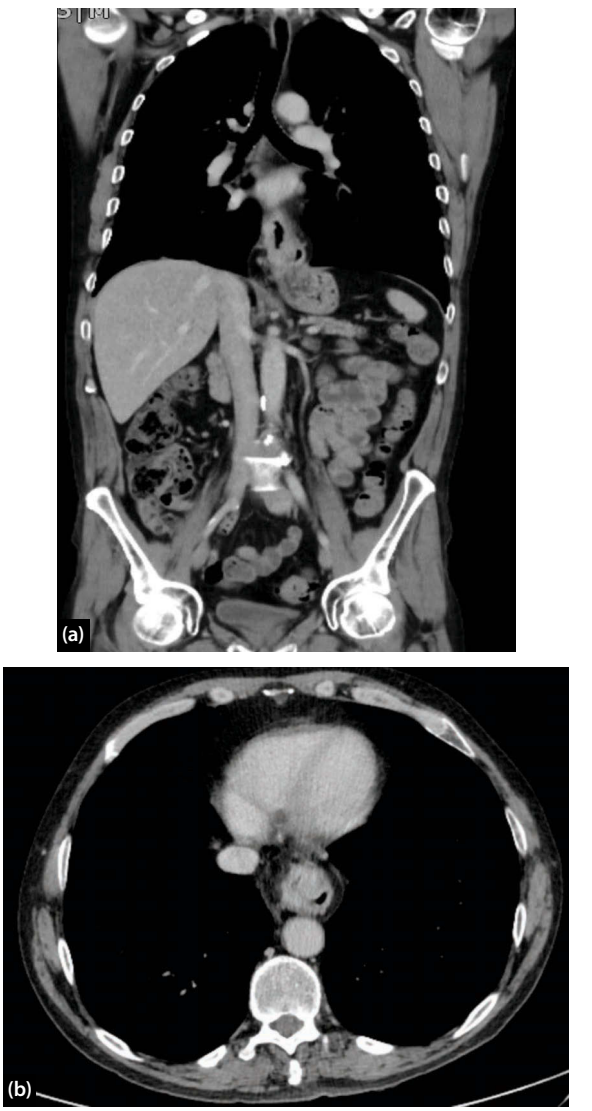

Figure 53.7 CT images demonstrating the presence of a polypoidal tumour in the lower oesophagus and a hiatus hernia.

BOX 53.2 Staging investigations in oesophageal cancer

All patients require endoscopy and CT. The majority also require endoscopic ultrasound and bone scan or PET-CT. Other investigations are selected on an individual case basis.

- Flexible videoendoscopy
- CT chest, abdomen, pelvis (gastric protocol)
- Endoscopic ultrasound
- Bone scan
- Positron emission tomography (PET-CT)
- Neck ultrasound +/– fine-needle aspiration
- Bronchoscopy
- Endobronchial ultrasound
- Staging laparoscopy
- Endoscopic mucosal resection

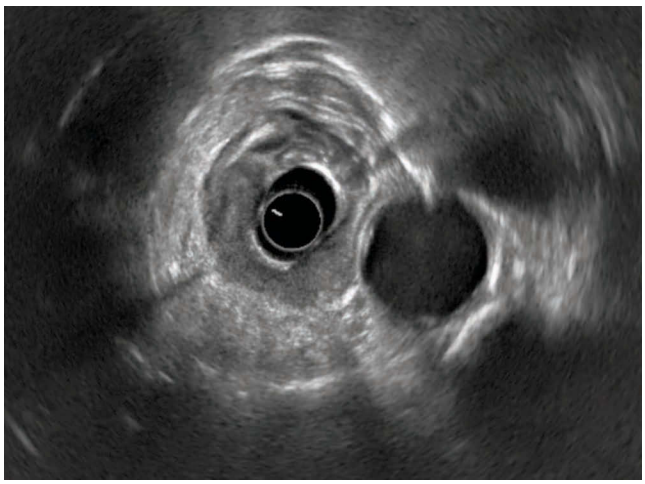

Figure 53.8 Endoscopic ultrasound image demonstrating a T3 oesophageal cancer posteriorly.

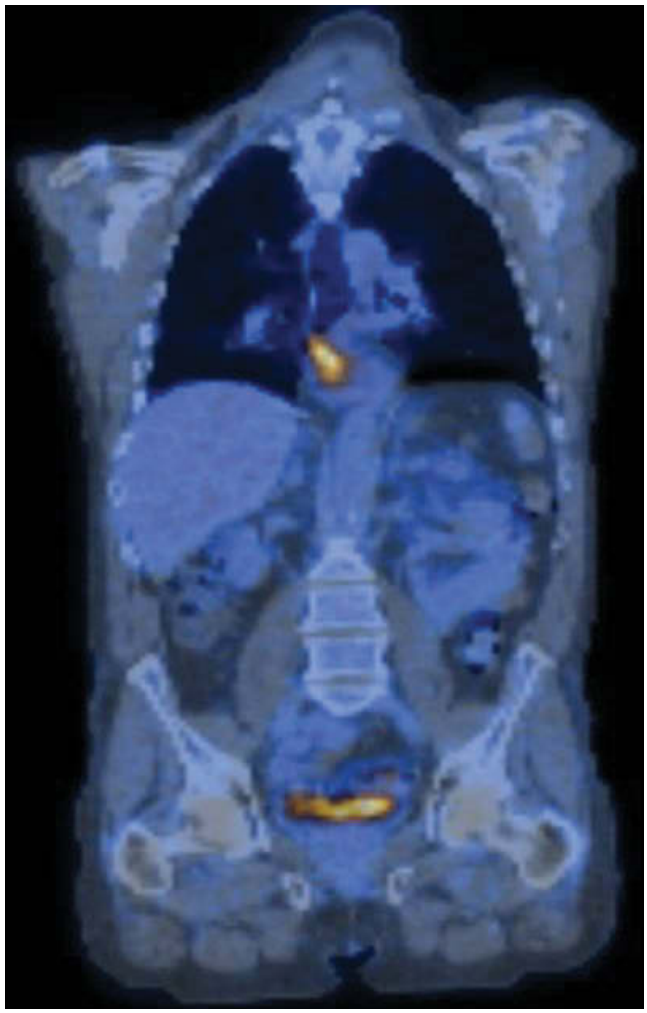

Figure 53.9 A PET-CT image demonstrating high uptake of FDG in a cancer of the lower oesophagus.

submucosa or to the muscularis propria where there is no evidence of nodal involvement on clinical staging (*c*T1/2 N0). Locally advanced cancers can be considered those cancers where there is evidence of lymph node involvement within surgically resectable fields or within the scope of radical radiotherapy in relevant cases of squamous cell carcinoma such that treatment is of curative intent.

NEOADJUVANT AND ADJUVANT CHEMOTHERAPY

For oesophageal cancer that is clinically staged as either reaching adventitia (T3/4) or with nodal involvement (N1-3), neoadjuvant chemotherapy or chemoradiotherapy followed by restaging and surgery is the recognized treatment pathway, with adjuvant chemotherapy then considered following surgery.

The benefit of chemotherapy was originally demonstrated by the Medical Research Council (MRC) OE02 study in which patients were randomized to receiving surgery alone or two cycles of cisplatin and 5-fluorouracil followed by surgery.[43] The patients who received neoadjuvant chemotherapy demonstrated an overall survival advantage of 6% at 5 years.[44] This regimen is currently still used in squamous cell carcinoma in the UK although is likely to be superseded by neoadjuvant chemoradiotherapy based on a similar chemotherapy regimen supplemented with neoadjuvant radiotherapy.

In oesophageal adenocarcinoma, neoadjuvant chemotherapy in the UK is based on the MRC adjuvant gastric infusional chemotherapy (MAGIC) trial that evaluated the benefit of administering three cycles of epirubicin, cisplatin and capecitabine in the neoadjuvant setting followed by a further three cycles in the adjuvant setting.[45] This trial was originally designed for gastric adenocarcinoma but included lower-third oesophageal and oesophagogastric junction adenocarcinoma. It demonstrated a 13% survival advantage at 5 years. A further study (OE05) comparing two cycles of neoadjuvant cisplatin and 5-fluorouracil to four cycles of epirubicin, cisplatin and capecitabine completed recruitment in 2011. A recent meta-analysis has confirmed the benefit of neoadjuvant chemotherapy.[46]

Current trials are assessing whether anti-angiogenic agents confer additional survival advantage, and preliminary investigations evaluating agents targeting growth factor receptor antagonists have also started.

NEOADJUVANT CHEMORADIOTHERAPY

Chemoradiotherapy in the neoadjuvant setting was previously reported in the UK but was abandoned in favour of neoadjuvant chemotherapy after reports of increased morbidity and mortality. Other countries continue to use neoadjuvant chemoradiotherapy, although regimens in each country differ. Newer chemoradiotherapy regimens do not appear to affect morbidity as in the past. Although there are few randomized trials comparing neoadjuvant chemotherapy to neoadjuvant chemoradiotherapy, a recent meta-analysis and a randomized trial suggest there is an additional survival advantage without an increase in morbidity.[47, 48] Squamous cell cancers are recognized as being more sensitive to chemoradiotherapy and most of the benefit highlighted in the recent trial was in patients with squamous cell carcinoma. Neoadjuvant chemoradiotherapy is likely to become the standard for squamous cell carcinoma. Whether the same occurs for oesophageal adenocarcinoma will depend on the outcomes of future appropriately powered studies designed to evaluate whether neoadjuvant chemoradiotherapy offers a survival advantage without additional morbidity to patients over neoadjuvant chemotherapy.

Surgery

The principles of oesophagectomy were established many years ago. Surgery is only undertaken with curative intent, when a complete (R0) resection is expected based on the staging investigations. There is no role for oesophagectomy in a palliative setting. An en bloc resection is performed with a radical two- or three-field lymphadenectomy.[49, 50]

LYMPHADENECTOMY

Current radiological staging investigations are not accurate enough to predict the lymph node status following resection in all patients. A standardized, radical lymphadenectomy is therefore performed in all patients to offer the best chance of cure. Evidence has accumulated that the extent of lymphadenectomy improves disease staging but more importantly improves overall survival and reduces locoregional recurrence rates.[51, 52] Patients in whom there is no evidence of nodal disease within the resection specimen are perhaps overtreated by the lymphadenectomy but this observation can only be made once all the lymph nodes have been examined by a pathologist. Patients with extensive nodal involvement are at high risk of having occult metastases and developing early recurrence. However, without the full lymph node resection for pathological analysis this cannot be determined. It must be remembered that for any given individual it is impossible to predict long-term outcome. The contribution of radical lymphadenectomy to the morbidity of oesophagectomy is difficult to quantify although the overall reduction in morbidity from resection and the improvements in lymph node yields suggest that in the majority of patients the lymph node dissection can be performed without additional burden.

In-hospital mortality following oesophageal resection has reduced to 2.9% in the UK while other major centres in the world also report improvements in mortality.[53, 54] This reduction is the result of a number of factors including earlier diagnosis, improvements in pre-operative patient assessment and selection, peri-operative care, and post-operative recognition and management of complications. Specialist oesophagogastric centres have been established that concentrate expertise and increase hospital and surgeon volume, with good evidence to suggest this approach improves outcomes.[55]

SURGICAL APPROACH[1]

The stomach is the preferred organ to use as the conduit following oesophagectomy. Colon is used in patients with previous gastric surgery rendering the stomach unsuitable or when there is extensive gastric involvement with the cancer. Either the right colon or transverse colon can be used. Colon is not considered as the primary choice owing to its functional deterioration over time. Jejunum can also be considered in certain circumstances.

Open surgery

Several different approaches can be used. For middle- and lower-third cancers, a two-stage transthoracic resection is the preferred approach. An upper midline incision is used, to allow for gastric mobilization with preservation of the right gastroepiploic and right gastric arteries and veins. A pyloroplasty or pyloromyotomy is performed to improve post-operative gastric emptying and reduce the risk of aspiration. Insertion of a feeding jejunostomy is also good practice and can be performed with a low additional complication rate. It allows enteral nutrition access during the recovery period but more importantly in the event of any anastomosis or conduit problems that delay the resumption of oral intake.

A posterolateral right thoracotomy is performed through the fourth or fifth intercostal space. The thoracic duct is removed en bloc along with all tissue dissected from the aorta, pericardium, pleurae, bronchi and right side of the trachea including all the mediastinal lymph node stations (**Figure 53.10**). A supra-azygous dissection is performed for middle-third oesophageal cancers or when staging investigations identify nodes above this level. It is not routinely required in lower-third cancers. The stomach is delivered into the chest, taking care not to twist the conduit. The stomach is divided to excise the cardia and proximal lesser curve with the oesophagus resection ensuring an appropriate margin from the primary tumour. The conduit must not be made too narrow as this will interrupt intramural vascular arcades and increase the risk of ischaemic necrosis of the anastomosis or conduit. The anastomosis is completed with a circular stapling device before closure of the gastrotomy. Hand-sewn anastomoses can also be used and there is no evidence to suggest either method is superior to the other.[56, 57]

A routine three-phase procedure with a neck dissection is not required unless the oesophageal lesion is in the upper

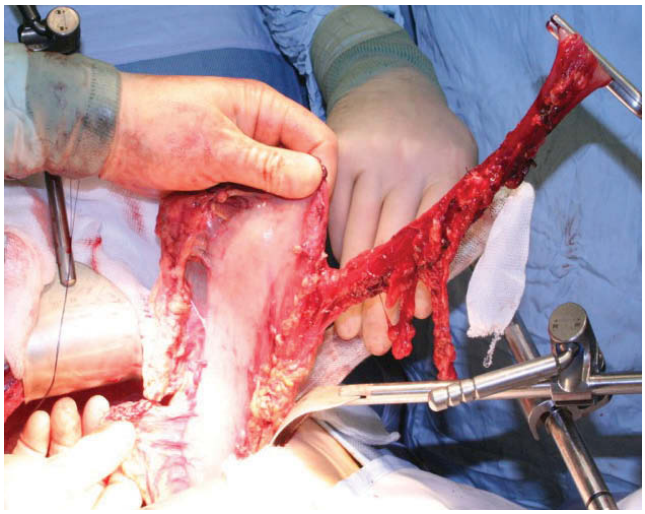

Figure 53.10 *En-bloc* resection of the oesophagus with delivery of the stomach into the chest prior to gastric division.

third or upper part of the middle third of the oesophagus. Routine three-field lymphadenectomy compared to two-field does not outweigh the potential increase in morbidity of the procedure from the extra thoracic dissection and neck dissection. Only minimal additional longitudinal resection is gained by this approach. Proponents highlight that cervical anastomotic problems cause less morbidity than intrathoracic leaks, although considerable reductions in overall anastomotic problems indicate that any such differences account for few patients. A left- or right-sided neck incision or a collar incision can be used to deliver the oesophagus and stomach into the neck and fashion an oesophagogastrostomy. Most surgeons use hand-sewn anastomoses in the neck although stapling techniques are also described.

Localized carcinoma of the hypopharynx or cervical oesophagus can be treated with pharyngolaryngo-oesophagectomy incorporating a radical neck dissection and a transhiatal oesophageal resection. Intraepithelial carcinomas of the upper oesophagus can also be considered for this approach.

Some surgeons approach lower- and middle-third cancers utilizing a left-sided thoracoabdominal incision. This route does not afford optimal access for either the formal abdominal lymph node dissection or the complete mediastinal lymphadenectomy. The transhiatal approach has a role in a selected group of patients. Some surgeons use this approach routinely although the ability to perform a radical mediastinal lymphadenectomy is considerably reduced. The technique has evolved from blind mediastinal dissection to several descriptions of dissection under vision.[58] Randomized trials comparing transhiatal and transthoracic resection have demonstrated improved survival in patients with oesophageal adenocarcinoma undergoing transthoracic resection, particularly in patients with limited nodal disease on histology.[30, 59]

Vagal-sparing resections and limited resections with jejunal interposition have been proposed as suitable alternatives for early disease on clinical staging.[30]

Minimally invasive oesophagectomy

Experience in minimally invasive oesophagectomy (MIO) techniques has increased over recent years, although publication of very few long-term results prevent definitive comparisons with open approaches.[60] It must be remembered that all the same oncological principles apply whether the adopted approach is open or minimally invasive.

Totally minimally invasive techniques involve laparoscopic gastric mobilization with thoracoscopic mediastinal dissection and oesophagus mobilization. Hybrid procedures utilize an open gastric mobilization and thoracoscopic mediastinal dissection, or a laparoscopic abdominal procedure followed by a conventional thoracotomy. The anastomosis can be performed in the chest through a mini-thoracotomy although is more commonly performed in the neck. The belief is that smaller incisions lessen the burden of the surgery on the patient, with less post-operative analgesia requirements, increasing mobilization and reductions in post-operative respiratory complications. One small, randomized trial has demonstrated a reduction in post-operative respiratory complication although it was not powered sufficiently to draw firm conclusions.[61] The UK national audit showed similar complication levels for open and MIO techniques.[54]

There are a few high-volume centres with experienced surgeons who achieve excellent results but this has not been reproduced countrywide. Complications specific to the MIO approach have been recognized including an increased risk of anastomosis and conduit problems. This has led to a refinement in techniques and an increase in the understanding of which patients are potentially suitable for such approaches. Overweight and obese patients create a particular challenge for laparoscopy due to the intra-abdominal fat obscuring tissue planes and the vascular arcade that requires preservation.

Robotic surgery has also been used in a few centres for oesophageal resection although such procedures remain in the remit of trials.[62] It will take many years to decide whether such techniques confer benefit in the recovery period without compromising long-term survival.

Endoscopic mucosal resection

Limited intramucosal disease where there is no evidence of nodal disease on CT or EUS can be resected using EMR. EMR is often performed as a diagnostic procedure but, provided depth of invasion is confined to the mucosa and both deep and lateral margins are clear, it can be considered a curative treatment. The procedure is performed under sedation. The submucosal layer is injected with Volplex®, indigocarmine dye and adrenaline. This lifts the lesion from the underlying muscle layer. The lesion is then removed either by applying suction and cautery with a cap device attached to the flexible endoscope, or by applying suction and a band below the lesion before excision (**Figure 53.11**).[63, 64]

Intensive endoscopic surveillance every 3 months is required with targeted biopsies at the EMR site to diagnose any dysplasia or recurrence as this is a relatively

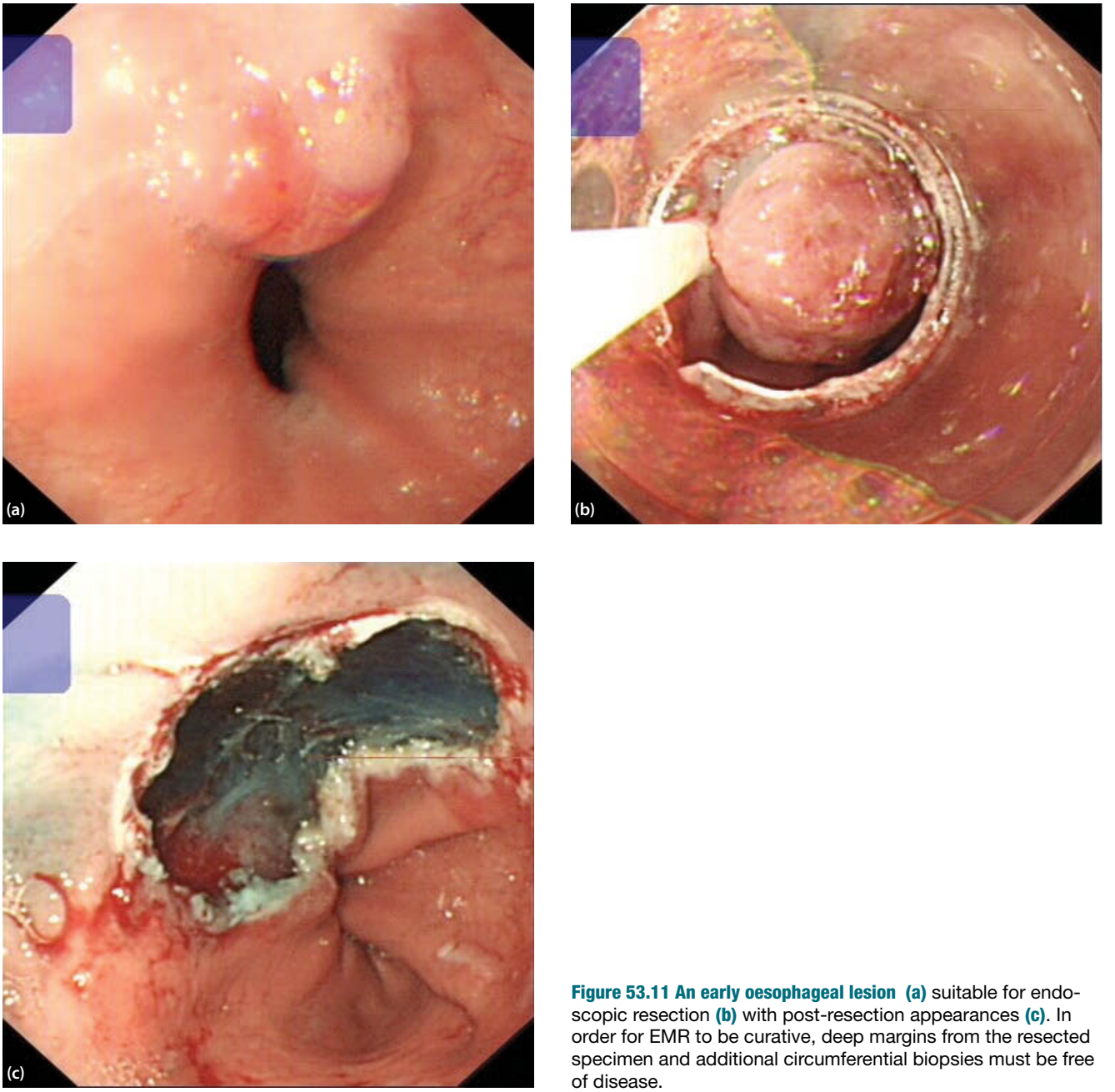

Figure 53.11 An early oesophageal lesion (a) suitable for endoscopic resection **(b)** with post-resection appearances **(c)**. In order for EMR to be curative, deep margins from the resected specimen and additional circumferential biopsies must be free of disease.

new treatment strategy and long-term results are few.[65] Evidence shows that the risk of lymph node metastases in the context of mucosal disease is negligible which is why this strategy has become feasible.[66, 67] If margins are positive, repeat EMR can be performed although surgery should also be considered. If circumferential margins are positive for dysplasia only (low-grade or high-grade) and all visible disease has been removed, the remainder of the oesophagus can be treated with RFA. Surgery should still be considered in young patients with high-grade dysplasia at the margins and in patients where there is evidence of multifocal high-grade dysplasia. Surgical resection is recommended because of the higher risk of lymph node involvement for oesophageal cancer with submucosal involvement although endoscopic submucosal dissection is technically feasible.

Definitive chemoradiotherapy

Definitive treatment with radical, concurrent chemoradiotherapy has been used with curative intent in oesophageal squamous cell carcinoma where total disease length does not exceed 10 cm. The evidence to compare this strategy to neoadjuvant treatment and surgery is sparse. No substantial evidence exists to support such an approach for adenocarcinoma. Often the choice of definitive chemoradiotherapy depends on the local expertise and the discussions between patient, clinical oncologist and surgeon. Patients who are not fit enough to undergo surgical resection might still be fit enough to tolerate definitive chemoradiotherapy. Studies have failed to identify conclusively for which particular patients definitive chemoradiotherapy might be a suitable curative option.

Salvage oesophagectomy remains an option in selected patients treated with definitive chemoradiation who fail to respond completely or demonstrate evidence of locoregional recurrent disease on follow-up.

Palliative treatments

Palliative chemotherapy and chemoradiotherapy can be used in patients with non-curative oesophageal adenocarcinoma and squamous cell carcinoma. External beam or endoluminal radiotherapy can be delivered to reduce tumour burden. Oesophageal stents are inserted to palliate dysphagia in patients with non-curative disease who are unsuitable for or opt against chemoradiotherapy.[68, 69] Stents should not be inserted in operable tumours because of the risks of perforation that would render the cancer incurable and also because of the transmural inflammation that inevitably results.

KEY POINTS

- Oesophageal adenocarcinoma continues to increase in incidence and accounts for the majority of oesophageal cancers in the Western world.
- Centralized units coordinate complete endoscopic and radiological staging with assessment of patient fitness through timed walking tests and cardiopulmonary exercise tests.
- Intramucosal disease might be suitable for endoscopic mucosal resection with follow-up endoscopic surveillance.
- Most patients with potentially curative disease have evidence of nodal disease or at least T3 depth of disease at presentation and receive neoadjuvant or peri-operative chemotherapy prior to surgery.
- Two-stage oesophagectomy with a radical lymphadenectomy has been shown to improve outcomes for lower-third adenocarcinoma.
- Experience with minimally invasive surgery techniques is increasing although a definite benefit has not been demonstrated and long-term outcomes are yet to be reported.
- Definitive chemoradiotherapy is an option in squamous cell carcinoma.
- Palliative treatments include chemotherapy, internal or external beam radiotherapy and endoluminal stents.

OESOPHAGEAL PERFORATION

Oesophageal perforation remains a rare condition and still has high mortality.[70] Spontaneous perforation (Boerhaave syndrome) occurs in an otherwise normal oesophagus.[71] Iatrogenic perforation can occur in a variety of procedures, particularly therapeutic flexible endoscopy, diagnostic or therapeutic rigid endoscopy or during revisional antireflux surgery. Increasing chances of a successful outcome depends upon a high index of suspicion, prompt resuscitation and investigation, with early transfer to a specialist oesophageal unit. The degree of pleural and mediastinal contamination in conjunction with the presence of systemic sepsis determines whether patients require surgery or can be managed non-operatively. Perforations of the cervical oesophagus are more likely to have successful non-operative management provided there is no mediastinal contamination. Non-operative approaches require intensive observation and reassessment of the patient (**Box 53.3**). A feeding jejunostomy can be inserted via a mini-laparotomy and is the preferred option for enteral nutrition access although a nasojejunal tube could also be considered.

BOX 53.3 Non-operative management of oesophageal perforation

- Nil by mouth
- Intravenous fluids
- Intravenous proton pump inhibition
- Intravenous antibiotics
- Intravenous antifungals
- Opiate analgesia
- Prophylactic low molecular weight heparin
- Nasogastric decompression (endoscopically or radiologically placed)
- Consider intercostal chest drain
- Enteral nutrition (feeding jejunostomy or nasojejunal tube)
- Regular reassessment in high-dependency environment

Surgery for perforation involves repair of the oesophageal defect following thorough debridement and lavage of mediastinal and pleural contamination of the mediastinum and pleura. Repair over a T-tube provides a controlled oesophagocutaneous fistula and is a good option in most, although primary repair has been used in some cases with success. Intercostal muscle flaps can be used as reinforcement. Oesophageal stents of varying types have been reported with varying success.[72] Stents are unlikely to hold position in an otherwise normal oesophagus, as there is not a stricture to hold the stent in place. Stents expose patients to complications of migration, bleeding and later stricture formation. They should not be inserted routinely in perforations as there is a lack of evidence to suggest healing rates and outcomes are improved. Many of the publications report on stent use in the context of adjunct drainage procedures. It is difficult to assess whether the control of sepsis through drainage or the stent contributes more to the healing in these situations.

KEY POINTS

- Recognizing oesophageal perforation requires a high index of suspicion.
- Prompt resuscitation, investigation and referral to a specialist centre are advised.
- The choice between non-operative and operative management depends on the degree of contamination and the presence of sepsis.
- Placement of oesophageal stents remains unproven and controversial.

FOREIGN BODY INGESTION

Ingested foreign bodies and food boluses can impact in the oesophagus. Foreign body ingestion is most commonly seen in children but also in patients with psychiatric conditions. Food bolus obstruction can occur in

any patient group. It is sometimes associated with an underlying Schatzki ring, peptic stricture or eosinophilic oesophagitis and occasionally is the first presentation of a malignant stricture. Initial investigations include antero-posterior and lateral plain radiographs, although some radiolucent objects will not be identifiable. CT can also be considered. Airway difficulties, absolute dysphagia, ingestion of sharp objects or button batteries, and prolonged impaction are indications for intervention. Rigid oesophagoscopy in experienced hands is appropriate to locate and retrieve impacted objects in the pharynx and cervical oesophagus. Care must be taken to avoid iatrogenic oesophageal perforation. Flexible endoscopy is the investigation of choice and allows for therapeutic intervention. It has a lower risk of perforation compared to rigid oesophagoscopy. Pushing a food bolus distally without having first passed the endoscope beyond the bolus should be avoided as it increases the risk of perforation.

MOTILITY DISORDERS

Achalasia

Achalasia is an uncommon condition with an annual incidence of 1 in 100 000. It is seen in both men and women, most frequently in middle and older age groups. Achalasia results from degeneration of the ganglionic neurons within the myenteric plexus and is characterized by a failure of relaxation of the lower oesophageal sphincter on swallowing with absence of peristalsis in the oesophagus. This can be associated with a higher resting tone in the oesophagus. Primary achalasia is idiopathic in aetiology while secondary achalasia occurs in Chagas' disease and following antireflux surgery with creation of a fundoplication wrap that is too tight.

PRESENTATION

Patients most often present with dysphagia to liquids and solids. Some present with symptoms of regurgitation or recurrent chest infections resulting from aspiration of stagnant oesophageal content. Retrosternal chest pain is a feature of a specific type of achalasia (vigorous achalasia) as a result of simultaneous, strong peristaltic contractions. Weight loss is a feature of long-standing achalasia.

INVESTIGATION

Investigation should start with a flexible endoscopy. It is important to exclude cancer as the underlying problem as many of the symptoms are common to both diagnoses. Endoscopic appearances in early achalasia can be completely normal. Features supporting a diagnosis of achalasia include a tight oesophagogastric junction, a dilated oesophagus or food within the oesophagus. A barium swallow in advanced cases will demonstrate delay in passage of barium across the oesophagogastric junction, possibly within a dilated oesophagus that fails to show any peristaltic activity (**Figure 53.12**). Confirmation of the diagnosis is provided by oesophageal manometry (**Figure 53.13**).

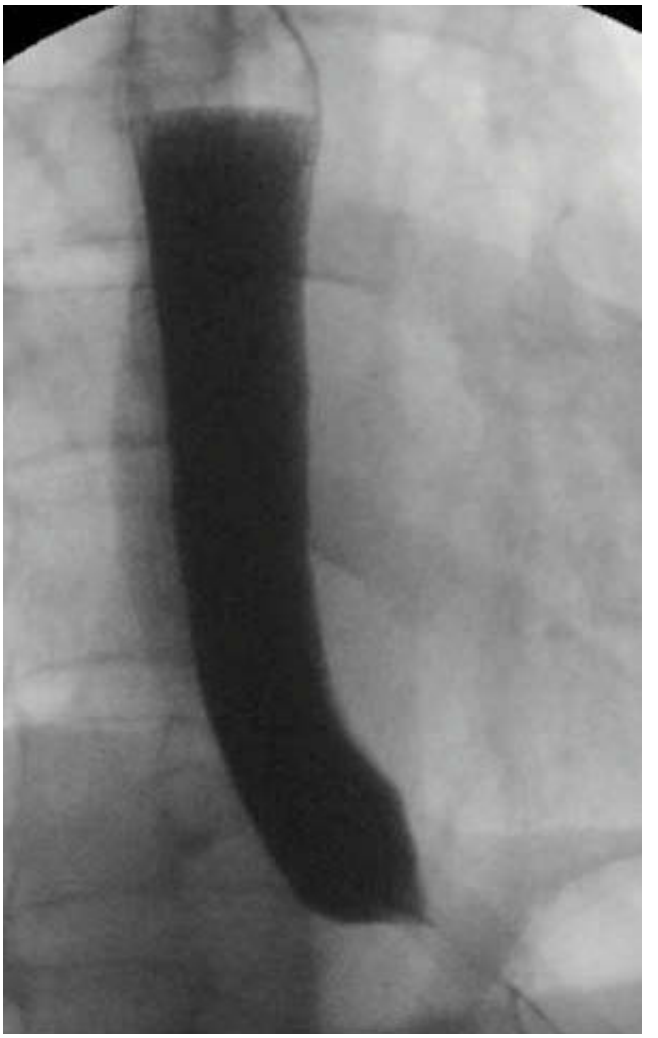

Figure 53.12 Barium swallow showing the classical bird's beak appearance in achalasia with a dilated, non-peristaltic oesophagus tapering towards a lower oesophageal sphincter that fails to relax.

Recent results with high-resolution manometry suggest there are several subtypes of achalasia that may respond differently to treatment.[73]

MANAGEMENT

The two main treatment options are endoscopic balloon dilatation or cardiomyotomy.[74–76] Results from a European multicentre randomized trial did not demonstrate differences in treatment efficacy at 2 years (93% balloon dilatation versus 90% laparoscopic cardiomyotomy) or in the occurrence of gastro-oesophageal reflux after treatment.[77]

Successful and safe balloon dilatation requires experienced endoscopists. The procedure is performed under sedation as a day-case procedure with image intensification used to ensure complete effacement of the balloon waist. The balloons are of fixed diameter with initial dilatation performed with a 30 mm size. Sequential dilatation can be performed if necessary after several weeks with a 35 mm and a 40 mm balloon. The main risk is of perforation and this risk increases with the larger diameter balloons.

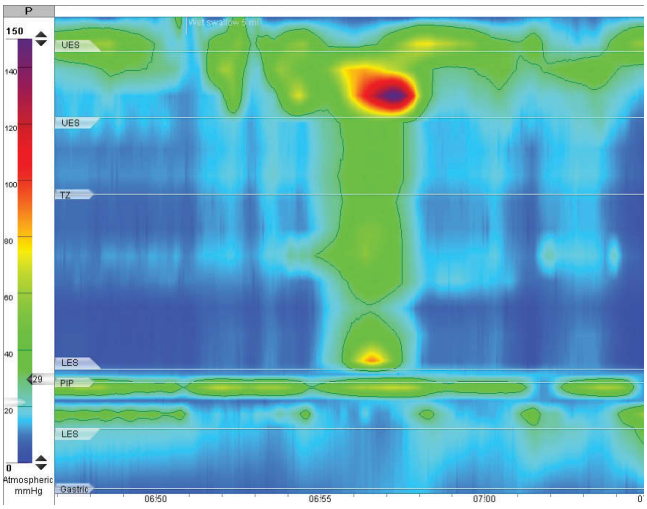

Figure 53.13 High-resolution manometry appearances of achalasia (type 2) with oesophageal compression. Pan-oesophageal pressurization can be seen in the oesophageal body between the higher pressure bands of the upper and lower oesophageal sphincters. The lower oesophageal sphincter fails to relax with swallowing.

Cardiomyotomy is performed laparoscopically and some surgeons combine this with a partial fundoplication intended to reduce the incidence of post-operative reflux.[78] The muscles are split for 5 cm along the oesophagus with the myotomy extended into the cardia for 3 cm. There is a risk of mucosal perforation with the procedure but this can be managed conservatively in most cases.

A newer technique of endoscopic myotomy has been developed in Japan and is being evaluated in randomized trials against balloon dilatation and cardiomyotomy.[79–81] It is performed under general anaesthesia and involves creation of a submucosal tunnel with an endoscope before division of the fibres in the circular muscle layer.

Endoscopic injection of botulinum toxin into the lower oesophageal sphincter is not a long-term solution. It has significant early failure rates and should be considered only in frail patients unsuitable for the other treatment modalities.[82]

SURVEILLANCE

Patients with achalasia should be enrolled on endoscopic surveillance programmes because of the increased risk of developing both squamous cell carcinoma and adenocarcinoma.[83, 84] Whether successful treatment alters this risk is currently not known.

KEY POINTS

- Achalasia requires investigation with endoscopy, barium swallow and manometry.
- Results from balloon dilatation and laparoscopic cardiomyotomy are equivalent so treatment depends on the available expertise.
- Achalasia patients should undergo endoscopic surveillance because of an increased risk of developing oesophageal cancer.

Diffuse oesophageal spasm

Diffuse oesophageal spasm is a rare condition characterized by non-peristaltic high-pressure contractions of increased duration. These occur in the smooth muscle of the lower two-thirds of the oesophagus. Symptoms are predominantly of severe retrosternal pain during swallowing and can occur in conjunction with dysphagia.

INVESTIGATION

Non-oesophageal causes of these symptoms need to be excluded. The diagnosis is evident on manometry when high-amplitude simultaneous contractions are measured within the oesophagus following an apparent normal swallow. This does rely upon patients experiencing symptoms during the 10 swallows of the investigation. Further investigation with ambulatory manometry might be required.[85] Occasionally evidence of such spasm is identified during a barium swallow.

MANAGEMENT

Treatment options aim to induce smooth muscle relaxation and include calcium channel blockers such as nifedipine, nitrates and botulinum toxin although results are variable. Surgery is rarely undertaken in these patients but one option is to perform a long oesophageal myotomy.[86]

Nutcracker oesophagus

This is a rare condition characterized by severe retrosternal pain during swallowing similar to diffuse oesophageal spasm. The diagnosis is made by demonstrating normal peristalsis with higher than normal amplitude contractions on manometry.

Eosinophilic oesophagitis

Eosinophilic oesophagitis is an increasingly recognized condition. Clinical symptoms relate to oesophageal dysmotility. Endoscopic features can include fixed oesophageal rings, luminal narrowing, furrows or exudates evident on flexible endoscopy.[87] Biopsies show eosinophilic infiltration within the oesophageal epithelium. Reflux disease should be excluded as the underlying cause. Treatment strategies are evolving and include topical steroids, avoidance of any identifiable food allergens and cautious dilatation of strictures.

Oesophageal diverticulae

Diverticulae are infrequently found in the oesophagus on flexible endoscopy. These are mostly asymptomatic. Congenital diverticulae are rare. Of acquired diverticulae, these are mostly of pulsion type where incoordinated peristalsis and functional obstruction lead to increased pressure at a specific point in the oesophageal wall. Most such diverticulae occur in the lower parts of the oesophagus and rarely need any specific treatment.

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All endoscopic and operative pictures are courtesy of Professor S Michael Griffin.

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CHAPTER 54

NEUROLOGICAL DISEASE OF THE PHARYNX

Kim Ah-See and Miles Bannister

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SEARCH STRATEGY

Data in this chapter may be updated by a Medline search using the keywords: pharynx, pharyngeal disease, neurological disorders and nervous system. Articles are included that are systematic reviews and meta-analyses of systematic reviews from four medical journals: *British Medical Journal*, *Lancet*, *New England Journal of Medicine* and *Journal of the American Medical Association*.

INTRODUCTION

A wide range of neuromuscular diseases can affect the pharynx. The primary function of the pharynx is swallowing. Different phases of swallowing are affected by different conditions, depending on which of the cranial nerves are involved. These diseases can also manifest as difficulties with breathing and speaking. Symptoms may arise in conjunction with anatomical variations, from congenital or acquired diseases.

ANATOMY AND PHYSIOLOGY

The reader is referred to a detailed discussion of the relevant anatomical details and physiology of swallowing in Chapter 47, Anatomy of the pharynx and oesophagus, and Chapter 48, Physiology of swallowing. A good understanding of these concepts is a necessary prelude to understanding management of neurological diseases of the pharynx.

SYMPTOMS

The principal symptoms of neurological dysfunction affecting the pharynx include:

- dysphagia
- odynophagia
- aspiration
- coughing
- choking
- throat clearing
- nasal regurgitation
- 'wet' voice.

Dysphagia is the principal symptom and can be due to a structural problem as well as a neurological one. History taking and physical examination are accompanied by endoscopy. Details of chronology, the effect of different food consistencies, exacerbating and improving factors and particularly past medical history help the clinician formulate a diagnosis. Oral cavity and cranial nerve examination are important in assessing neurological disease of the head and neck. Examination of the face and limbs can elicit muscle wasting and fasciculation.

EXAMINATION

General examination of the patient can yield information about the likely underlying pathology for the reported swallowing difficulties. Paucity of facial expression suggests Parkinson's disease whereas facial weakness and grade of this suggests a stroke and the time elapse since onset. Inspecting for mobility aids (walking stick, walking

frame, wheel chair) and a tracheostomy also provides an indication of disease severity that may relate to the degree of swallowing dysfunction.

Patients' gait patterns may correspond to certain neurological diseases. A festinating gait can be characteristic of Parkinson's disease as can a broad-based gait in cerebellar dysfunction. Fatigability can accompany advanced Myasthenia gravis, though will also be present in patients with advanced osteoarthritis and those with intermittent claudication secondary to peripheral vascular disease.

Certain distinctive patterns of speech may be present in those patients with advanced cases of neurological disease. Dysarthric (slurred) speech is the commonest speech pattern present in neurological disease and is associated with cerebrovascular accidents, cerebellar disease, Parkinson's and motor neurone disease. 'Wet' or 'moist' speech can develop in patients with Parkinson's disease due to poor oral phase control, though this does develop in cases of head and neck trauma and presbyphagia. It is usually associated with aspiration. Patients' suffering with bulbar palsy (affecting the IXth, Xth, XIth and XIIth cranial nerves) can develop a nasal quality to their speech. The aetiology of this condition is primarily a lesion of the medullar oblongata, though local tissue infarction and demyelinating diseases are also causes. Those with pseudobulbar palsy may demonstrate 'Donald Duck' speech due to alaryngeal vocalization using the buccal area.

Formal neurological examination may or may not elicit the signs described later in this chapter. Cranial nerve examination, particularly of the lower cranial nerves, provides the most useful and familiar assessment to the otolaryngologist in this area. Unilateral or bilateral fasciculation or even wasting of the tongue or soft palate, secondary to progressive deinnervation of the muscles will affect the oral and pharyngeal phases of swallowing. Flexible nasolaryngoscopy is useful in identifying these changes in the pharyngeal constrictor muscles and identifies other abnormalities including vocal cord palsy, polling within the pyriform fossae and laryngeal penetration that contribute to the overall assessment of patients' swallowing abilities.

INVESTIGATIONS

Swallowing assessment and endoscopy

Swallowing assessment is complemented by functional endoscopic evaluation of swallowing (FEES). The pharynx and larynx are visualized through an endoscope while boluses of different volumes and consistencies are swallowed. These endoscopies may be performed at bedside, if tolerated by the patient, limiting the need for transport to a radiology department, possibly in a different hospital.[1] Images may be recorded and transferred for discussion and review. FEES may be performed by appropriately trained speech and language therapists. Views of bolus and saliva retention in the hypopharynx can be achieved, which may not be possible in videofluoroscopy.[1] The disadvantages are obstruction of the operator's view due to food and fluid in the pharynx and when the pharynx closes, limiting assessment of the pharyngeal phases of swallowing. The oesophageal phase cannot be viewed either, though the upper oesophageal lumen can be visualized.

Videofluoroscopy

Videofluoroscopy is the gold-standard investigation in assessing neurological disease of the pharynx. Videofluoroscopy was initially developed in 1965 and involves recording fluoroscopic images that appear on a monitor of a patient ingesting a radio-opaque bolus.[2] This demonstrates the dynamics of the swallowing mechanism and allows speech and language therapists to assess swallowing problems and identify techniques for a safer swallow for the patient.

The investigation can identify nasal regurgitation, poor pharyngeal contraction, retention of the food bolus within the vallecula and pyriform sinus, and problems with opening of the upper oesophageal sphincter. Videofluoroscopy is particularly useful in identifying 'silent' aspiration, pre-, intra- and post-deglutitory.[1]

The patient is placed in an anterolateral position and anatomical landmarks are identified. Administration of the bolus begins with minimum quantities to avoid the risk of inhalation and may be increased as the consistency of the patient's swallow is assessed. Liquid, semi-liquid and solid boluses can be provided. An anteroposterior image recording can assess for asymmetry in movement or stasis of the bolus.[1]

Radiation exposure is limited in videofluoroscopy and the recorded images can be viewed repeatedly and transferred between clinicians and centres.[1] It supplements the clinical examination in those patients with reflex mandibular closure and aids treatment planning.[3] 'Reflex mandibular closure' is different from the gag reflex and is a sign of neurological disease, whereby patients are unable to maintain mouth opening, rather than reacting to oropharyngeal stimulation. No direct view of the passage of the food bolus is provided, however, and videofluoroscopy cannot be performed at the patient's bedside, requiring transfer to a radiology department. The general physical state of the patient may prevent investigation and compliance with instructions. Interpretation of the images recorded may vary considerably.[1]

ACQUIRED CONDITIONS

NEUROMUSCULAR DISEASE

Multiple sclerosis

Multiple sclerosis results from inflammatory demyelination of neurons within the central nervous system. Progressive and relapsing–remitting forms of the disease have been identified, the former of which generally has a poorer prognosis. The greatest incidence is in younger adults, particularly those of Western European origin and in areas between latitudes 40°N and 40°S. Definite diagnosis requires evidence that two or more areas of the central nervous system are affected on different occasions.

Cerebrospinal fluid testing may reveal oligoclonal bands of immunoglobulin G.

Dysphagia results when the brainstem and/or the corticobulbar tracts are affected. Dysphagia typically presents in advanced cases of the disease, while choking is more a feature of the earlier stages. Percutaneous gastrostomy feeding may therefore be required. Videofluoroscopy reveals a delayed swallowing reflex and loss of pharyngeal peristalsis.

Management includes corticosteroid medicines and β-interferon. While multiple sclerosis itself is not a terminal condition, many sufferers succumb to pneumonia due to poor coughing mechanisms and uraemia as a result of urinary retention and renal failure.

Parkinson's disease

Parkinson's disease results from degeneration of the substantia nigra in the zona compacta, leading to a reduction in the neurotransmitter dopamine within the brain. Symptoms develop around 45–65 years of age. The disease is overwhelmingly idiopathic without any aetiological cause, though manganese, carbon monoxide and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) narcotic can be implicated in its development. Diagnosis is based primarily on the clinical features displayed by patients including rigidity, bradykinesia, tremors and poor posture stability.

Swallowing initiation slows and bolus stasis in the pyriform fossae results.

Levodopa remains a mainstay of treatment as do anticholinergic agents and dopamine agonists. Selegiline and amantadine inhibit dopamine metabolism and improve milder symptoms, respectively. Catechol-O-methyltransferase (COMT) inhibitors reduce levodopa metabolism, prolonging the effect. Deep brain stimulation surgery is available.[4]

Myasthenia gravis

Myasthenia gravis results from autoimmune IgG antibodies developing against acetylcholine receptors at the end plate of the neuromuscular junction. Nerve impulse conduction is slowed and weakened as a result. Voluntary muscle weakness develops with diplopia and ptosis in cases of orbital muscle involvement. Classically symptoms are reported to improve following periods of rest and worsen with periods of repetitive action. Patients may present with dysphagia, dysphonia or nasal regurgitation alone having previously been well and deterioration in symptoms correlates with advancement of the disease. Electrophysiology testing reveals muscle fatigue following stimulation and serum acetylcholine receptor antibodies may be detected.

Videofluoroscopy reveals reduced pharyngeal mobility and aspiration.

Management includes cholinesterase inhibitors, edroponium, corticosteroids and other immunosuppressive agents. Thymus excision may benefit those patients with a thymoma because of the causative effect of the tumour.

Motor neurone disease

Motor neurone disease describes a collection of diseases that affect motor nervous fibres, including progressive bulbar palsy, pseudobulbar palsy, primary lateral sclerosis, amyotrophic lateral sclerosis and progressive spinal muscle atrophy. Difficulties in swallowing, chewing, coughing, talking and breathing develop in addition to limb weakness, limb stiffness, muscle wasting and fasciculation. Motor neurone disease is progressive with death most commonly resulting from pneumonia.

Dysphagia and aspiration result if the corticobulbar tract is affected. The disease is aggressive (death from the amyotrophic lateral sclerosis results within 5 years of symptom onset) and early gastrostomy insertion should be considered to prevent aspiration pneumonia, as dysphagia develops within months of diagnosis or may be the presenting symptom.

Guillain Barré syndrome

Guillain Barré syndrome, also described as acute idiopathic polyneuropathy, results from multifocal demyelination of the cranial nerves and immune cell-mediated damage to nerves, usually following a preceding infection or immunization. Both motor and sensory function deteriorates, usually in an ascending and symmetrical pattern with peripheral regions of the body being affected initially. Motor function deterioration is usually more prominent. Respiration and swallowing function can be affected, though not universally.

Cerebrospinal fluid analysis reveals high protein concentrations. The prognosis is generally good though recovery may be prolonged. Up to 20% of sufferers may be left with residual disability.

Muscular dystrophy

Muscular dystrophy is a collection of myopathic disorders that result in muscle wasting. This leads to continued muscle contraction following withdrawal of the initial nerve impulse producing further muscle weakness. Duchenne muscular dystrophy has the worst prognosis with rapid progression; death results within 15 years of symptom onset due to respiratory failure and pneumonia when the respiratory muscles become affected. Other types are more benign with slower rates of progression. Muscle biopsy and electromyography confirm the myopathic nature of the disease.

The soft palate is usually affected with regard to swallowing, producing dysphagia and nasal regurgitation. Sensation is maintained. Videofluoroscopy reveals muscle paralysis leading to nasal regurgitation and aspiration. No treatment for muscular dystrophy exists though physiotherapy and speech and language therapy maintain function and slow symptom progression.

STROKE

Cerebrovascular events are the commonest neurological disorders of the pharynx. Patients may suffer with

both dysphagia and aspiration. Nerve injury results from infarction or, less commonly, haemorrhage. Patients typically present with sudden onset of neurological deficits, the signs of which reflect the area of the brain affected. Patients commonly have a past medical history of atherosclerosis, hypertension, diabetes mellitus or heart valve disease. Infarction risk is uniform throughout the cerebral vasculature.

Dysphagia can be the sole symptom of an event affecting the brainstem, with videofluoroscopy demonstrating asymmetrical movement and poor bolus transit. CT imaging of the head distinguishes between an infarction and haemorrhage. Management involves anti-platelet therapy and control of risk factors to prevent reinfarction in particular, including statin use to reduce blood cholesterol levels.[5–7] Thrombolysis has an increasing role in treating ischaemic strokes that present sufficiently early. Patients may be suitable for carotid artery surgery if symptoms are transient, which may be offered as an urgent or emergency operation.[8] The overall prognosis for survival is better for those suffering an ischaemic than a haemorrhagic stroke, though the risk of recurrence is greater in such patients, as is the risk of myocardial infarction.

INFECTIOUS DISEASE

Polio

Polio is caused by poliovirus that destroys neurons within the anterior horn cells of the spinal cord. The brainstem may also be affected. Dysphagia develops slowly and steadily when the pharyngeal muscles are affected, often years after the original infection. The disease is rare in the developed world but remains endemic elsewhere, such as in parts of Asia and Africa.

Herpes zoster

Herpes zoster results from *Varicella zoster* virus infection, which remains in the dorsal root ganglia and cranial nerve ganglia in a latent state. Reactivation can lead to palsies of the lower cranial nerves. Disease manifestation is commoner in patients over 60. Treatment includes famciclovir or acyclovir antiviral agents. The disease has equal prevalence throughout the world.

Diphtheria

Diphtheria results from *Corynebacterium diphtheria* bacterial infection, which produces a neurotoxin that can ultimately lead to pharyngeal weakness. Infection of the pharynx may also cause airway obstruction. The treatment includes antitoxin and penicillin antibiotics. A vaccination based on the toxin is available. The disease is commoner in the developing world.

Rabies

Rabies is caused by a viral infection residing in feral animals. The virus infects the neurons of the central nervous system, through which it spreads. Laryngopharyngeal spasm can result as can fasciculation of the pharyngeal muscles. This severely limits the patient's ability to swallow, leading to aspiration. Rabies has been eradicated in much of the developed world but is endemic elsewhere. It can be successfully treated with vaccination and specific immunoglobulin administration.

Botulism

Botulism results from bacterial toxins released from *Clostridium botulinum* that weaken the muscles supplied by the lower cranial nerves. Patients present with dysphagia. The disease can be successfully treated with a specific antitoxin.

NEOPLASTIC DISEASE

Nasopharyngeal carcinomas and particularly skull-base tumours compress and invade the lower cranial nerves producing a variety of symptoms. MRI and CT scanning of the anterior cranial fossa, brain and temporal bone should follow the appropriate clinical examination. Surgery or radiotherapy can then be considered. A variety of jugular foramen syndromes exist, described in **Table 54.1**. A small number of paraneoplastic syndromes have been associated with neurogenic dysphagia including squamous cell carcinoma of the skin, transitional cell carcinoma of the bladder, ovarian cancer, prostate cancer and chronic lymphocytic leukaemia.[9–13]

MISCELLANEOUS ACQUIRED CONDITIONS

Trauma and surgery

Blunt or penetrating trauma to the pharynx can injure the nervous supply as well as cause structural abnormalities through muscle injury. Iatrogenic surgical injury in thyroid, cardiothoracic, anterior cervical spine, carotid and oesophageal surgery can injure branches of the vagus nerve in particular.

TABLE 54.1 Jugular foramen syndromes

Syndrome	Cranial nerves affected	Aetiology
Vernet's	9, 10, 11	Aneurysms or tumours at the jugular foramen
Collet–Sicard	9, 10, 11, 12	Parotid tumours, chemodectomas or metastases at the posterior laterocondylar space
Villaret's	9, 10, 11, 12 Horner's syndrome	Parotid tumours, chemodectomas or lymphadenopathy at the posterior retroparotid space
Jackson's	10, 12 Corticospinal tract	Chordomas, metastases or schwannomas

Glossopharyngeal neuralgia

Glossopharyngeal neuralgia presents with stabbing pain in the oropharynx region innervated by the glossopharyngeal nerve. The cause is unknown but the symptoms may be attributed to Eagle's syndrome. Investigation for skull-base lesions may be required and, while surgery to remove an enlarged styloid process may treat the condition in cases of Eagle's syndrome, symptom control is usually achieved with carbamazepine.

Medication

Medications whose side effects result in depression of the central nervous system can make any dysphagia worse.

Old age

The oral phase of swallowing increases in old age and the first two stages become 'uncoupled', leading to the food bolus passing into the vallecula prior to laryngeal elevation. The food bolus volume necessary to stimulate pharyngeal swallowing may need to increase up to five times. Both these factors increase the risk of aspiration.

CONGENITAL CONDITIONS

A small number of neurodevelopmental disorders affect the function of the pharynx. Compression of nervous tissue is the principal cause of pharyngeal dysfunction.

In Klippel–Feil syndrome, the cervical vertebra fuse during growth, compressing the brainstem and injuring the nuclei of the lower cranial nerves, with concurrent shortening of the neck. In Dandy–Walker syndrome, cerebrospinal fluid flow out of the ventricular system is obstructed, leading to a cyst developing in the posterior cranial fossa that compresses the cortex and brainstem. Compression of the brain by an Arnold–Chiari malformation can cause brainstem herniation and injury. In syringomyelia, a cystic cavity remains in the medulla or upper spinal cord that enlarges to compress and injure the nerve tracts.

TREATMENT

The treatment of neurological disease of the pharynx centres on accurate diagnosis of the underlying cause and treatment of that cause. Specific otolaryngological interventions for those chronic conditions that cannot be treated centres on avoiding aspiration, with resulting pneumonia, and maintaining feeding. Both require a multidisciplinary approach and a crucial role is provided by speech and language therapists.

A variety of techniques can be deployed to these ends. Solid food chewing is preferable to liquid foods that are more easily aspirated. Neck flexion both aids swallowing and protects the airway. The Mendelsohn manoeuvre aids the opening of the pharyngo-oesophageal segment and coughing immediately after swallowing clears food from the laryngeal inlet, preventing aspiration. More detail on the subject of rehabilitation is presented in Chapter 55, Rehabilitation of swallowing disorders.

Support to control sialorrhoea medically is available.[14] Hyoscine (usually in patch form), glycopyrrolate (usually as oral solution) are most commonly used in the United Kingdom and are anticholinergic medications that antagonise the effects of acetylcholine at the muscarinic receptors. Other medications used are atropine, tropicaimide, hyoscyamine and tricyclic antidepressants, which all have anticholinergic properties.[14] Common side effects include xerostomia, urinary retention confusion and sedation and anticholinergic use is contraindicated in glaucoma and in those patients with established dementia.

Botulinum toxin (type A or type B) can be injected into the major salivary glands to reduce saliva production by inhibiting acetylcholine release from axonal endings at cellular neuromuscular junctions.[14] The dosage and duration of effect are variable but can be repeated. Ultrasound guidance improves gland localization, particularly in those that undergo atrophy with age or from repeated injection, and the accuracy of delivery.

Those patients who cannot tolerate swallowing safely will require a feeding tube to be placed. Short-term feeding needs can be satisfied with insertion of a nasogastric tube but patients with chronic or deteriorating swallowing problems with little hope of recovery will benefit more from a gastrostomy placement. Feeding usually takes place overnight for convenience to the patient.

Anxiety and depression must be recognized in patients at every stage of their problems and should be treated accordingly.

There is a specific role for surgery to 'normalize' the phases of swallowing. Vocal cord medialization techniques can aid airway closure in swallowing while cricopharyngeal myotomy or botulinum toxin injection into the muscle will treat spasm of the cricopharyngeus muscle. Tracheostomy insertion abates the risk of aspiration but interferes with the normal process of swallowing by fixing the position of the larynx. Rarely, total laryngectomy may need to be considered to eliminate intractable aspiration.

KEY POINTS

- The aetiology of neurogenic dysphagia and the clinical features of different neurological diseases should be considered when managing swallowing disorders.
- FEES assessment and videofluoroscopy are complementary in the assessment of patients' swallowing function.
- The management of neurogenic dysphagia is multidisciplinary and includes treatment of the principal aetiology, early speech and language therapist input to improve swallowing function and ensure a 'safe' swallow and consideration of additional interventions to prevent aspiration and maintain satisfactory feeding and nutrition.

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CHAPTER 55

REHABILITATION OF SWALLOWING DISORDERS

Maggie-Lee Huckabee and Sebastian Doeltgen

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SEARCH STRATEGY

Data in this chapter are based on several independent literature searches of the PubMed, Scopus and Google Scholar databases, which involved relevant keywords describing each intervention (e.g. effortful swallow, transcranial magnetic stimulation, transcranial direct current stimulation etc.) and outcome measure (e.g. pharyngeal pressure, motor evoked potential etc.). Furthermore, the reference lists of identified studies were searched for additional relevant publications.

INTRODUCTION

The clinical management of swallowing disorders has evolved over the last four decades to include ongoing development of compensatory and rehabilitative interventions designed to increase swallowing efficiency and safety. Initially, the clinical approach to managing swallowing disorders was largely characterized by strategies to compensate for impaired peripheral motor function. Many of these techniques remain a valuable asset in the clinical armamentarium for the short-term management of disordered swallowing. Since then, multidisciplinary clinicians and researchers have developed ever-increasing sophistication and specificity in the diagnosis and treatment of dysphagia. As diagnostic specificity is increasing, we are no longer applying traditional treatment approaches to patients in a 'one size fits all' approach.

Increased specificity will ultimately lead to improved rehabilitative outcomes, for two reasons. First, with greater diagnostic specificity we will be able to tailor compensatory and rehabilitative efforts to directly address the underlying impairment of any given patient. One example of this is the clinical application of a technique known as thermal–tactile application (TTA) of the faucial pillars. This technique was originally developed to facilitate initiation of pharyngeal swallowing[1] and was applied to any patient presenting with preswallow pharyngeal pooling. It stands to reason that only patients presenting with pharyngeal pooling secondary to sensory impairment would benefit from this sensory-based technique, not those presenting with underlying motor impairment. Thus, careful scrutiny of the underlying impairment and consequent selection of the right treatment for the right problem is likely to increase the rehabilitative effectiveness of TTA.

Second, increasing diagnostic precision will improve patient outcomes by decreasing the likelihood for causing harm. For example, the technique of effortful swallow, historically applied as a compensatory technique to facilitate bolus clearance during swallowing,[2, 3] is now increasingly being used as a rehabilitation approach.[4, 5] Repeated swallowing with effort is presumed to strengthen pharyngeal contraction, much like repeatedly lifting weights will increase arm muscle strength. However, studies have now demonstrated that effortful swallowing may in fact impair, not facilitate, anterior hyoid movement during swallowing in some patients due to an imbalance of anterior and posteriorly oriented forces acting on the hyolaryngeal complex during swallowing.[6] A subsequent case study has documented the potential for effortful swallowing to impair movement patterns at the base of the tongue, resulting in nasal redirection.[7] Similarly, the Mendelsohn manoeuvre was originally designed to increase airway protection through volitionally prolonging swallowing-related suprahyoid contraction at the point of maximal hyolaryngeal excursion.[3, 8] Recent evidence obtained using high-resolution pharyngo-oesophageal manometry demonstrates that, while pharyngeal bolus passage may be aided by increased and prolonged pharyngeal pressure generation, proximal oesophageal peristalsis is significantly decreased

during Mendelsohn manoeuvre swallows.[9, 10] Meticulous evaluations of both short- and long-term effects of these manoeuvres, and others, are required.

Our current state of the art in dysphagia rehabilitation is quickly broadening from an almost exclusive approach of peripheral muscle strengthening to incorporate techniques designed to maximize central control mechanisms. This chapter provides a cursory introduction to the established muscle-strengthening techniques for which a supportive evidence base has been reasonably established. Then we look ahead with a preview of exciting new developments in cortical modulation that are likely to move into clinical application once a supporting evidence base is available.

CURRENT REHABILITATION APPROACHES

Oral motor exercises

Speech pathology has a long history of therapeutic efforts aimed at increasing the strength and efficiency of oropharyngeal movements. Originally, these were developed for improving articulatory precision related to speech. Subsequently, these exercises were logically expanded and transferred to swallowing rehabilitation, with the goal of improving oral phase movements and facilitating tongue-driving forces involved in pharyngeal phase swallowing. Although these techniques have been around for decades, only recently has their efficacy for improving functional swallowing been systematically investigated. The development of a handheld manometric device, known as the Iowa Oral Performance Instrument (IOPI), facilitated the evaluation of oral motor exercise (OME) in swallowing rehabilitation. Regular OME using this device and performed prophylactically by healthy elderly individuals can increase swallowing and isometric peak pressures following a 9-week exercise regimen.[11] This was accompanied by an increase in lingual volume. Of note, the beneficial effects of regular OME do not necessarily rely on using the IOPI for training; they can also be achieved by standard tongue strength exercises using a tongue depressor.[12] A study evaluating the effects of OME in patients documented that an 8-week isometric lingual exercise regimen using IOPI as biofeedback modality increased isometric and swallowing pressures for some bolus conditions in patients presenting with dysphagia following stroke.[13] It has also been demonstrated that tongue strength measured using the IOPI is significantly correlated with oral phase dysphagia following stroke[14] and longer meal times in residential age care.[15]

Effortful swallow

First introduced as a compensatory technique by Kahrilas and colleagues,[2, 3] the instructions for this technique are simply to 'swallow hard'. With increased effort resulting in increased pressure on the bolus, this technique was routinely applied to reduce pharyngeal residue in patients with pharyngeal motility disorders. A considerable body of research has documented the potentially positive effects of increased pharyngeal pressure associated with effortful swallowing.[6, 9, 10, 16–24] However, subsequent research now demonstrates that simply 'swallowing hard' is not as benign as it may seem.

A potential complication of the effortful swallow was documented to be decreased anterior hyoid movement during swallowing.[6] Biomechanically, this observation is likely linked to the relative imbalance in the opposing muscles that act on the hyoid during swallowing. Anterior pull of the relatively small floor of mouth muscles may be outweighed by posteriorly oriented forces exerted by the much larger pharyngeal constrictors and suprahyoid muscles (posterior belly of digastric, stylohyoid). Due to the synergistic coordination of the oropharyngeal swallowing process, it is likely that during effortful swallowing, **all** muscles involved in swallowing exert a greater degree of contraction. With regard to the movement of the hyolaryngeal complex, this would lead to a biomechanical imbalance resulting in a stronger net posterior hyoid displacement compared to non-effortful swallows. A further single case study of a young patient with brainstem tumour resection experienced increasing nasal redirection on initiation of effortful swallowing that subsided when the technique was discontinued.[7] In young healthy women, effortful swallowing was shown to increase sympathetic cardiac modulation, a sign of cardiac overload.[25] These studies require replication but should prompt clinicians to understand that, if a technique is powerful enough to effect a positive change, it may also be powerful enough to effect a negative change. It is critical to understand which direction our interventions take on not only the physiological feature of interest but other biomechanical and (neuro-)physiological processes as well.

Mendelsohn manoeuvre

Another technique, which was originally introduced as a compensatory technique but which is now being employed as a rehabilitative approach, is Mendelsohn manoeuvre.[8] Following initiation of swallowing, peak hyolaryngeal excursion is maintained for several seconds before relaxing and completing the swallow. The presumed benefit of this manoeuvre is prolonged suprahyoid contraction, which subsequently results in prolonged upper oesophageal sphincter (UOS) opening for improved bolus flow into the oesophagus. Repeated performance of this manoeuvre is now thought to result in improved cricopharyngeal compliance. In 1990 Logemann and Kahrilas[8] were the first to report the biomechanical effects of the Mendelsohn manoeuvre in a single case report of a patient presenting with dysphagia following lateral medullary infarct. Swallowing efficiency improved greater than twofold over other techniques in this patient. Subsequent basic research identified increased duration of anterior and superior hyolaryngeal excursion that resulted in delayed UOS closure on videofluoroscopic swallowing study. Miller and Watkin[22] later identified similar results using real-time ultrasound, and a further study employing manofluorography suggested that not only the duration but also the

intensity of pharyngeal contraction is increased during this manoeuvre.[26] McCullough and colleagues documented that, following 2 weeks of treatment, 18 patients with dysphagia following stroke demonstrated increased duration of hyoid excursion[27] and increased hyoid elevation,[28] which were not maintained after a subsequent 2-week, non-training period. Of note, two studies employing high-resolution pharyngo-oesophageal manometry in healthy volunteers demonstrated that, while pharyngeal pressures and bolus transfer were increased during Mendelsohn manoeuvre swallows, proximal oesophageal peristalsis was reduced.[9, 10] This phenomenon requires consideration in clinical populations with impaired pharyngo-oesophageal peristalsis and warrants further investigation.

Masako manoeuvre

The Masako, or tongue-hold manoeuvre, is the first potential rehabilitation exercise that was designed to directly address a specific underlying symptom. Fujiu and colleagues initially documented significantly increased anterior bulge of the posterior pharyngeal wall in patients who had undergone base of tongue resection for cancer treatment. [29] The Masako manoeuvre was designed to mimic this disorder by instructing individuals to 'protrude the tongue maximally but comfortably, holding it between the central incisors'.[30] In healthy participants, this manoeuvre resulted in videographically assessed increased anterior bulging of the posterior pharyngeal wall.[30] This manuscript provided a caution, however, about using this technique during bolus ingestion as the anterior tongue placement leaves the airway in a relatively unprotected, vulnerable position. When the technique was translated to a small population of three patients with base-of-tongue resection, the manoeuvre resulted in increased base-of-tongue to posterior pharyngeal wall contact pressures. This finding is remarkable considering that the posterior pharyngeal wall was required to compensate for the anteriorly resected base-of-tongue structures. In a group of 40 healthy individuals, however, oropharyneal and hypopharyngeal pressures did not differ during manoeuvre conditions, while UOS relaxation pressures were significantly reduced.[31] Using high-resolution pharyngeal manometry and intramuscular electromyography, it was similarly demonstrated that, in the absence of posterior tongue movement during tongue-hold swallows, activation of the superior pharyngeal constrictor was increased, resulting in stable pharyngeal pressures.[32]

Head-lift (Shaker) exercise

The Shaker exercise was originally introduced by Shaker et al.[33] and was designed to target floor-of-mouth muscle contraction outside the context of swallowing with the aim of increasing UOS opening during ingestion. Individuals are instructed to lie flat on their back and to raise their head until they can see their feet, without raising their shoulders off the bed. As such, this exercise is purely a muscle-strengthening exercise for the floor-of-mouth muscles involved in both the oral phase (lowering the jaw during chewing) and pharyngeal phase (contraction of floor-of-mouth musculature and subsequent anterior displacement of the hyolaryngeal complex) of swallowing. Importantly, this exercise does not strengthen other muscles involved in swallowing, as is the case with the effortful swallow or Mendelsohn manoeuvre. Research has documented that the Shaker exercise induced signs of fatigue in the floor-of-mouth muscles[34] and increased EMG amplitude during exercises,[35] suggesting an active involvement of these muscle during the exercise. In their initial study, Shaker et al. documented that this exercise resulted in increased laryngeal excursion, increased width and duration of UOS opening and consequently decreased UOS intrabolus pressure in healthy elderly individuals. Similar findings were reported in a subsequent study of stroke patients and patients with specific impairment of UOS opening.[36] After 6 weeks of exercise, all were able to resume oral feeding. Clinically, it is conceivable that this exercise may be a suitable addition to training with the effortful or Mendelsohn manoeuvres as it specifically targets the swallowing musculature and may hence counteract any biomechanical imbalance potentially induced by the latter two manoeuvres (as discussed above).

Expiratory muscle strength training

Expiratory muscle strength training (EMST) is quickly emerging into more widespread clinical practice and is a promising approach for pharyngeal swallowing impairment and airway protection. EMST emerged from the area of respiratory medicine and has since been adapted for speech and swallowing rehabilitation. EMST is designed to strengthen the contraction of the expiratory musculature by directing expiratory airflow through a one-way, spring-loaded valve that remains open in the presence of positive airflow. The resistance of the valve can be adjusted so that increasing valve resistance requires increasing expiratory airflow. Initial work by Sapienza et al.[37] demonstrated that EMST resulted in significantly increased expiratory airflow in young, healthy participants. Proof of concept for a potential application of EMST in swallowing rehabilitation was provided by a study that documented increased activation of floor-of-mouth muscles during EMST. As outlined above, these muscles play a critical role of providing anterior pull on the hyolaryngeal complex during swallowing which biomechanically facilitates UOS opening. Based on the promising early results, several studies of the effects of EMST in neurological populations have since documented that EMST may help recover respiratory muscle weakness in Parkinson's disease[38, 39] with a further study demonstrating greater hyoid movement and penetration–aspiration (P–A) scale scores following a period of EMST training.[40] Positive effects have also been reported in patients with multiple sclerosis on speech production and, importantly, strength of voluntary cough in patients with moderate disability.[41, 42] Similarly, EMST has been shown to increase maximum expiratory pressure and maximum hyoid displacement during swallowing in amyotrophic lateral sclerosis.[43]

EXPANDING THE INTERVENTION REPERTOIRE

As outlined in the previous section, the majority of interventions available for swallowing rehabilitation have traditionally focused on facilitating the recovery of swallowing function through biomechanical modifications that are largely driven by increased muscle strength. The assumption has persisted that, by increasing peripheral muscle strength, there would be consequent increased biomechanical force, which in turn would facilitate effective pharyngeal bolus clearance and airway protection. This approach may well be appropriate in some presentations of swallowing impairment; however, it may also well be inappropriate in others. By focusing solely on peripheral, biomechanical (dys)function, there has been little regard for the central neurological networks that drive human sensorimotor function. This represents a significant shortcoming in common management practices for patients with neurological impairment.

Increased understanding of swallowing neural control – particularly the role of the cerebrum in swallowing neural networks – has brought about a significant paradigm expansion in our collective approach to addressing swallowing impairment. Recent research favours the assumption that, if we can modify the underlying neurological substrates of swallowing, the changes in swallowing biomechanics will be more permanent and robust than what is seen following peripheral muscle exercise alone. Behavioural and non-behavioural techniques for neural modulation are currently under development and provide promise for new approaches to rehabilitation of swallowing impairment. These are briefly outlined below, accompanied by a discussion of ethical and practical challenges that may accompany their transition into routine clinical practice.

Behavioural, cortical modulation: skill training paradigms

Stevenson and Allaire[44] comment that a process of encephalization underlies the ability to modify the reflexive swallowing response seen in infancy to the more mature and variable response seen in adult-like, ingestive swallowing. Inherent in this comment is the suggestion that the 'skill' component of swallowing is acquired through cortical expansion and modulation of the primitive brainstem generated response. Quite unlike our current strength-based, peripheral approaches, relearning or modifying the complex sequence of swallowing events at the level of central control is gaining increasing recognition as a type of skill-based training following neurological impairment.

DEFINITION AND REQUIREMENTS OF SKILL TRAINING

Much of the conceptual research related to skill training derives from physiotherapy. In very brief summary, this research suggests that task-oriented skill-training programmes produce more favourable rehabilitative effects on recovery of motor impairments than strength-training programmes due to greater neuroplastic adaptation in the motor cortex,[45] greater corticomotor excitability,[46] greater functional movement improvements[47] and greater strength gains.[48]

Skill training can be defined as the acquisition of skill through functional repetition and refinement of movement patterns. However, fundamental knowledge of neurorehabilitation demands that mere repetition of a task will not improve skill; several additional criteria must be met. First, skill-based training must incorporate task-specificity to ensure cortical plasticity.[49] Thus any repetitive exercise must replicate the desired task – in this case swallowing. Second, there must be an element of task challenge and problem solving[50] to activate different brain circuits which underlie motor learning, neural and behavioural change.[51] Finally, extrinsic visual and intrinsic kinaesthetic feedback regarding task performance allows for evaluation of movement accuracy and correction on subsequent exercise trials.[52, 53]

EARLY ATTEMPTS AT TRANSLATING TO SWALLOWING RESEARCH

Translated to clinical routines, some of our traditional strength training approaches may indeed satisfy the task-specificity requirement by incorporating repetition of exercise into the context of functional swallowing; this would be the case with effortful swallowing, Mendelsohn manoeuvre, or tongue-hold swallowing. The adaptation required for task execution lends support for their application in skill-based training regimes with the focus on initiation and modulation of volitional swallowing rather than strengthening. Inclusion of ingestive swallowing in the treatment paradigm also meets the criteria for task specificity. However, there is likely to be very little therapeutic benefit from ingestion of a safely tolerated diet as it merely repeats a task with no challenge. The newly described McNeill Dysphagia Therapy Program[54] could be considered a type of skill training as it meets the requirement of task challenge. This protocol uses a hierarchical approach to bolus size and texture, thus systematically challenging oral intake in a controlled therapeutic environment. Another approach using surface electromyography as a biofeedback device has recently been described.[55] Although historically used to provide valuable feedback regarding increased strength of contraction, recent research suggests great benefit of this modality for increasing skill and precision of movement using a targeted, skill-based rehabilitation protocol[55] This protocol meets the characteristics of skill training by requiring repeated execution of skilled swallowing movements, progressive and challenging aims for timing and degree of muscle contraction, and ongoing and delayed feedback regarding task performance.

Proof of concept research in a sample of patients with dysphagia secondary to Parkinson's disease has documented significant improvements in quality of life and functional swallowing after two weeks of daily skill training. Other skill training approaches have been explored using manometry as a biofeedback device to alter timing characteristics of the pharyngeal response[56] and respiratory related feedback to improve swallowing respiratory coordination.[57]

Our past rehabilitation attempts that have focused on strength training may well have inadvertently facilitated recovery by increasing skill, more so than strength. Only recently have clinicians and clinical researchers focused specifically on therapeutic tasks to increase swallowing skill with the exclusion of potential imbalance in the biomechanical system through muscle strengthening. In doing so, rehabilitative outcomes are likely to improve as we develop greater specificity in treatment options.

Non-behavioural or behaviourally augmented central modulation: stimulation paradigms

The development of brain imaging and stimulation techniques has significantly expanded our understanding of the neurophysiological mechanisms of swallowing. Approaches designed to improve swallowing function through extrinsic modulation of central neuronal circuits involved in swallowing motor control have received increasing interest by researchers and clinicians alike. Approaches designed to improve swallowing function through extrinsic modulation of central neuronal circuits involved in swallowing motor control have received increasing interest by researchers and clinicians alike. A growing body of evidence now suggests that harnessing the brain's ability to reorganize its synaptic connections using stimulation techniques may in the future provide superior rehabilitation outcomes in some patient groups compared to 'traditional' behavioural intervention.[58, 59] Techniques developed to assess and promote neuroplastic reorganization in the human motor cortex, including transcranial magnetic stimulation (TMS), transcranial direct current stimulation (tDCS) and pharyngeal electrical stimulation (PES) will be briefly outlined below. At present, none of these techniques has been sufficiently evaluated in order to be applied in routine clinical practice; however, their evidence base is continuously expanding. Once optimal treatment paradigms have been developed and evaluated, it is highly likely that some, if not many, of these techniques will be available to the judicious clinician.

The reader is directed to Doeltgen and Huckabee[60] for a discussion of some of the practical and ethical considerations that accompany the transition of these techniques into routine clinical application. It is worth noting that several brain stimulation devices are already available for anyone to purchase over the internet.[61] This is likely to speed up the transition of some of these techniques into clinical practice and may challenge their application in an evidence-based framework.

TRANSCRANIAL MAGNETIC STIMULATION

Perhaps the most researched non-invasive brain stimulation technique in the field of swallowing rehabilitation is that of transcranial magnetic stimulation (TMS). Employing a strong but short-lasting electric current that is discharged through a coil of wires placed over a targeted cortical area, usually the primary motor cortex, a magnetic field is generated that painlessly penetrates the intact skull. At sufficiently high intensities, TMS transynaptically activates descending motor output neurons that in turn will generate descending volleys of action potentials. These can be measured at the periphery as a single motor-evoked potential (MEP) using surface electromyography. In its basic application, single-pulse TMS therefore allows assessment of the excitability of targeted motor circuits. Rapid application of up to several hundred TMS pulses, known as repetitive TMS (rTMS), can under certain circumstances modulate the trans-synaptic excitability of the targeted motor circuits and this effect may outlast the stimulation period by several hours.[62] The nature of the neuroplastic changes induced by rTMS heavily depends on its stimulation parameters, including frequency, intensity and stimulus pattern.

Conventional rTMS is applied in rhythmical trains of single stimuli. When applied at low inter-stimulus frequencies of less than 1 Hz, rTMS reduces corticospinal or corticobulbar excitability, whereas higher rTMS frequencies of greater than 1 Hz increase it. For example, in healthy research participants, 1 Hz rTMS applied over the motor projections to the pharyngeal musculature reduces the corticobulbar excitability of these projections, which is accompanied by a reduction in swallowing reaction time of normal and fast swallowing.[63] Although significant in its own right due to its proof of principle nature, this finding may be particularly important for future studies developing this paradigm into a rehabilitation approach for patients who present with delayed onset of swallowing, such as following stroke. Interestingly, when facilitory 5 Hz rTMS was applied to the non-dominant hemisphere, the inhibitory effects of the previous 1 Hz rTMS could be reversed, an effect that was shown to restore swallowing function.[64]

In a group of patients presenting with dysphagia following stroke, 5 Hz rTMS applied over the contralesional hemisphere was shown to increase pharyngeal motor cortical excitability, which was accompanied by a reduction in aspiration scores and pharyngeal residue.[65] In contrast, low-frequency 1 Hz rTMS applied over the ipsilesional hemisphere clinically increased swallowing response time for liquids and reduced aspiration for liquids and residue for paste on videofluoroscopy.[66] Applied at 3 Hz over the lesioned representation of the oesophageal musculature, rTMS resulted in improved clinical presentation of swallowing impairment in cortical stroke patients[67] and patients presenting with lateral medullary stroke or brainstem stroke.[68] Taken together, the findings of these studies suggest that rTMS may hold the potential to assist the recovery of swallowing function in various patient groups, although at present the variability in stimulation paradigms is reflective of the infancy of this approach.

TRANSCRANIAL DIRECT CURRENT STIMULATION

Although it has been developed over a century of invention and research,[69, 70] electrical stimulation of the human

central nervous system has only recently been rediscovered in the form of transcranial direct current stimulation (tDCS). Unlike its relatively painful relative, transcranial electrical stimulation, tDCS employs low-intensity electrical direct currents that modify the excitability of large neuronal assemblies mainly through changes in the transmembrane potential during stimulation. In general, anodal current flow applied over the primary motor cortex increases the excitability of its motor representations, whereas cathodal stimulation has the opposite effect. Originally demonstrated in the corticospinal motor system,[71] the bidirectional effects of tDCS have now also been demonstrated in the corticobulbar motor system involved in the control of swallowing. For example, cathodal tDCS at 1.5 mA intensity for 10 minutes reduced pharyngeal motor excitability, whereas 10 minutes of 1.5 mA or 20 minutes of 1 mA of anodal tDCS increased it.[72] When applied in a cohort of patients presenting with cortical stroke, 2 mA contralesional anodal tDCS applied for 30 minutes combined with effortful swallowing on 5 consecutive days increased functional swallowing based on clinical presentation.[73] Likewise, ipsilesional application of 1 mA anodal tDCS for 10 days[74] or 5 days[75] improved clinical ratings of swallowing function.

Several systematic reviews come to the conclusion that both rTMS and tDCS may hold a promising potential to assist the recovery of swallowing function. The reader is directed to these reviews for an in-depth discussion of the currently available evidence.[76–79] It is worth noting that in these clinical trials researchers evaluated the effects of the various tDCS paradigms on clinical outcome measures that were based purely on observational, clinical rating scales. Future studies are warranted to evaluate neurophysiological and biomechanical outcome measures underlying the reported clinical improvements.

PHARYNGEAL ELECTRICAL STIMULATION

Pharyngeal electrical stimulation (PES) differs from non-invasive brain stimulation techniques in that it is not applied directly to the central nervous system. Instead, a weak electrical current is applied to the sensory receptors of the pharyngeal mucosa via surface electrodes embedded in a catheter.[80] This technique deserves mention as it has been systematically evaluated in several seminal studies in both healthy and swallowing-impaired populations. The cumulative evidence so far suggests that this approach may provide a suitable means of modifying the excitability of corticobulbar projections relevant for swallowing. When applied using optimal stimulus parameters,[80] increased excitability of the pharyngeal cortical motor representation was accompanied by an improvement in dysphagic symptoms, including pharyngeal transit times and aspiration scores.[81] Similarly, a single application of PES in a group of patients presenting with chronic stroke resulted in an increase in corticobulbar excitability of the unaffected hemisphere and was associated with a decrease in aspiration scores.[82] The neuroplastic effects induced by PES appear to have a cortical origin[80] and may be modified by genetic influences.[81] Based on these preliminary findings, PES may be a promising alternative to non-invasive stimulation techniques that are directly applied to cortical neuronal tissues, especially in patients who meet exclusion criteria for these techniques.

NON-INVASIVE BRAIN STIMULATION IN THE CONTEXT OF EVIDENCE-BASED PRACTICE

The transition of any new intervention from the research laboratory into routine clinical practice will naturally need to occur within the framework of evidence-based practice. Sackett et al. define this as the synthesis of external research evidence, internal clinical expertise of the treating clinician and client preferences.[83] As outlined in this chapter, a growing body of external scientific evidence presently outlines the promising potential of peripheral or central stimulation techniques targeting swallowing-related neuronal networks to support swallowing rehabilitation efforts. Further large-scale clinical trials are required to establish optimal stimulation paradigms and to test these for their safety and efficacy. The judicious clinician will eventually be able to incorporate this knowledge into their own clinical reasoning and guide their clients towards making fully informed decisions. In recognition of our responsibilities regarding beneficence and non-maleficence in research and clinical practice, this process will occur gradually and within the framework stipulated by the Declaration of Helsinki (2013).

SWALLOWING REHABILITATION – A RAPIDLY CHANGING LANDSCAPE

As outlined in this chapter, swallowing rehabilitation practices are undergoing a significant and rapid expansion from focusing solely on modification of peripheral biomechanics towards understanding and harnessing the neurophysiological mechanisms that underlie human swallowing. As such, researchers and clinicians are challenged to address the required cultural, ethical and organizational issues that accompany the development of novel skill-training and brain-stimulation techniques. These challenges include questions regarding the provision of neuromodulatory interventions to patients, determination of professional competencies and scope of practice as well as practical implications for patient services.[58] Partnerships between stakeholders across the various professions involved in swallowing rehabilitation will facilitate the development of required institutional frameworks locally and globally. Unrestricted access to information via the internet has accelerated the transition from bench top to routine clinical application in many areas of health services. It is therefore likely that patients will increasingly become more vocal stakeholders in the clinical decision-making process than perhaps has previously been the case. It will be the responsibility of clinical service providers to guide their patients in this process by providing individually tailored, evidence-based advice.

KEY POINTS

- Swallowing rehabilitation practices have traditionally focused on enhancing oropharyngeal swallowing biomechanics primarily through muscle strengthening exercise.
- With increased recognition of the role of the cortex in modulating swallowing behaviour, contemporary approaches to rehabilitation are shifting attention from muscle strengthening to the capacity for control adaptation.
- Skill-based behavioural training approaches are emerging that maximize voluntary volitional control, with early research seeking to define this type of treatment and provide proof of concept outcomes.
- Neuromodulatory approaches that employ cortical and peripheral non-invasive neurostimulation techniques are being actively researched with preliminary evidence to suggest that certain non-invasive brain stimulation protocols can improve some aspects of dysphagia.
- The development of competency and regulatory frameworks will be required to facilitate the transition of novel behavioural and neuromodulatory approaches to clinical practice.

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CHAPTER 56

CHRONIC ASPIRATION

Guri S. Sandhu and Khalid Ghufoor

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SEARCH STRATEGY

Data in this chapter may be updated by a PubMed search using the keywords: dysphagia, aspiration, unsafe swallow, cricopharyngeal dysmotility, pharyngeal pouch and laryngeal incompetence.

INTRODUCTION

The larynx, trachea and bronchi form the conduit between the lungs and the external environment through which respiratory gases are transported and pulmonary secretions are expectorated. The larynx is also the primary organ of phonation, acts to protect the airway from aspiration during swallowing and provides important sensory feedback and movements that are critical to the control of ventilation.[1] Swallowing is a highly complex process, both voluntary and involuntary, requiring the precise coordination of many different muscle groups through the actions of sensory and motor nerves via the central nervous system.

Charles Darwin noted in *On the Origin of Species* that the human is the only animal whose upper aerodigestive tract fails to adequately serve its principal evolutionary functions of preventing aspiration and acting as the gateway to the lungs.[2] In all mammals, including the human infant, the pharyngeal airway is short and the epiglottis and the soft palate are anatomically related, allowing simultaneous swallowing and breathing. Starting at 4–6 months of age, the larynx descends in man, leading to loss of nasolaryngeal association. The neonate's larynx lies at the level of the 3rd cervical vertebra and the adult larynx lies at the level of the 6th cervical vertebra. This adult position allows humans to meet the requirements of complex speech through resonance and articulation.

Aspiration is contamination of the tracheobronchial tree with secretions, food material and other contaminants. Prevention of aspiration occurs primarily through reflex laryngeal closure, laryngeal elevation and cessation of breathing during swallowing, and any aspirated contents are expelled through coughing. A certain amount of aspiration is normal in humans, especially during sleep,[3] but is tolerated without complications in healthy subjects with normal tracheobronchial ciliary function and normal immunology.

The response to even small quantities of aspiration will depend on the pH of the aspirate, microorganisms present and the person's pulmonary and immunological status. This may lead to cough or in some cases life-threatening pulmonary complications. In cases where the cough reflex is reduced or absent, 'silent' aspiration may occur. Acute severe aspiration of a large bolus may lead to airway obstruction and may prove fatal, whereas chronic small

volume aspiration may risk pneumonia or respiratory failure through chronic pulmonary emphysematous disease or bronchiectasis.

Chronic or intractable aspiration is usually associated with a significant impairment of the normal swallow, especially if there is a dysfunction of the larynx or pharynx.

PRESBYPHAGIA

Although it is widely believed that swallowing function deteriorates with age, the evidence supporting this is inconclusive, especially if one excludes the affects of neurological disorders, diabetes mellitus and connective tissue diseases.[4] The changes in swallow function with age appear to be modest but there does appear to be a reduction in the swallowing function reserve and 'plasticity', lowering the threshold for dysphagia and aspiration, and impairing the success of swallowing therapies, manoeuvres and corrective surgery.

Swallowing is a complex process that requires finely coordinated neurological inputs and is therefore susceptible to a variety of structural and neuromuscular diseases.[5–7]

EVALUATION OF THE 'ASPIRATING PATIENT'

All patients with severe swallowing problems and aspiration should be assessed and managed in a multidisciplinary setting. This team should include an otolaryngologist with a special interest, swallowing therapist, gastroenterologist, neurologist and dietitian, and have access to appropriate radiology and respiratory medicine.

A thorough history from the patient, relative or referring physician will often reveal the cause of the aspiration.

Physical examination is essential and must include examination of the head, neck and upper aerodigestive tract with functional assessment of the cranial nerves.

Flexible nasal endoscopy in the clinic will help exclude tumours and masses as well as determine laryngeal function and sensation. The signs may be subtle, with even small quantities of pharyngeal residue or secretions indicative of a swallowing problem. At the other extreme there may be significant pooling of secretions, bathing an oedematous, asensate larynx and freely entering the airway.

Videofluroscopic (VF) assessment of swallowing should always be performed in conjunction with a swallowing therapist. The investigation provides valuable information about the nature of the swallowing disturbance and degree of aspiration. Ideally it is performed using limited amounts of barium but where there is clinical suspicion of aspiration then a water-based radiological contrast agent should initially be trialled.

Functional endoscopic evaluation of swallowing (FEES) uses dyed liquids, semi-solids and solids, which are sequentially swallowed with nasopharyngeal fibre-optic observation and video recording. Swallowing strategies can be trialled and recorded during the assessment. The technique will diagnose aspiration but has the added advantages that it avoids radiation and can be performed by the bedside. In addition, it can be viewed with the patient, and provides biofeedback to the patient regarding the benefits of swallowing strategies and manoeuvres.

Objective assessment tools for aspiration are available. The Penetration-Aspiration Scale[8] uses data from FEES and VF studies, and the New Zealand Index for Multidisciplinary Evaluation of Swallowing (NZIMES)[9] and the MBS Measurement Tool for Swallow Impairment (MBSImp)[10] rely on data from VF. The most widely accepted subjective score for dysphagia is the Eating Assessment Tool (EAT-10).[11]

PRINCIPLES OF MANAGEMENT

The aims are to protect the airway, avoid life-threatening respiratory complications and achieve adequate nutrition, while also considering the psychological and social aspects of food and feeding. As previously mentioned, these patients should be assessed and treated in a multidisciplinary team environment.

TABLE 56.1 Causes of an unsafe swallow

Neurological and neuromuscular disorders	Auto-immune disorders	Damage to larynx, pharynx or neck	Others
• Cerebrovascular accidents • Head injuries • Hypoxic brain injuries • Parkinson's disease • Amyotrophic lateral sclerosis • Multiple sclerosis • Motor neurone disease • Muscular dystrophy • Myasthenia gravis • Guillain-Barre syndrome • Myopathies • CNS tumours • Neurosurgery or skull-base surgery	• Systemic sclerosis (scleroderma) • Bullous mucosal conditions • Systemic lupus erythematosis • Sjögren's syndrome and salivary gland diseases	• External trauma (RTA or sports injuries) • Internal trauma (caustic ingestion) • Reflux diseases • Post-surgical (conventional and trans-oral laser) • Post-irradiation • Neoplasms • Strictures	• Intoxication or drugs • Eosinophilic oesophagitis • Pharyngeal pouch • Cricopharyngeal muscle discoordination/ spasm • Achalasia • Severe illness or nutritional deficiencies • Amyloidosis

Under the direction of the swallowing therapist, where possible, compensatory techniques, dietary modification and appropriate exercises should be trialled (discussed in Chapter 66, Speech/voice therapy for voice disorders). Medical therapy should be directed at dealing with the underlying cause of the dysphagia. Excessive secretions sometimes respond to the use of anticholinergic patches but these may be associated with unacceptable side effects. Alternatively, ultrasound guided botulinum injections to salivary glands[12] may be considered.

The oral phase of swallowing is quite complex and attempts at surgical restoration, usually following cancer surgery, at best create a mass of tissue to optimize any residual function with compensatory techniques. Surgery for swallowing is generally limited to the pharyngeal or oesophageal phases and even then it can only be directed at specific sites contributing to the dysphagia or aspiration. In many cases surgery is not possible because of the very poor health of the patient or poor prognosis, or because a surgically correctable cause is not identifiable.

Progressive deterioration of swallowing function, leading to aspiration, can be assessed at intervals in the multidisciplinary swallowing clinic and appropriate investigations, therapies or procedures can be directed for the best possible quality of life for the patient. Patients may present acutely with severe aspiration, usually following an acute neurological event. A bedside assessment is usually adequate to identify those in whom oral intake should be discontinued and an alternative route of nutrition provided. Initially this will be via a small nasogastric feeding tube but where recovery is unlikely, or is likely to take many days or weeks, then a gastrostomy feeding tube should be considered. Antibiotics and pulmonary physiotherapy should be commenced where appropriate.

Nasogastric and gastrostomy feeding tubes will not eliminate aspiration of secretions and further consideration needs to be given to airway protection. A tracheostomy tube with a low-pressure cuff allows airway toilet in patients with copious secretions; however, current cuff design does not eliminate the passage of secretions into the lower airway.[13] The tracheostomy tube also reduces laryngeal elevation by 'anchoring' the trachea, and the inflated cuff compresses the oesophagus,[14] resulting in partial obstruction (**Figure 56.1**). In addition the tracheostomy reduces the effectiveness of the cough, and bypassing the normal flow of air through the larynx may reduce laryngeal sensitivity. On intensive care units there is increasing use of tracheostomy tubes with a suction port above the cuff, reducing the risk of secretion aspiration.

A tracheostomy tube is therefore not the ideal solution to chronic aspiration and when used for this purpose will require close attention and frequent suctioning of the oropharynx and tracheostomy, especially in the debilitated patient.

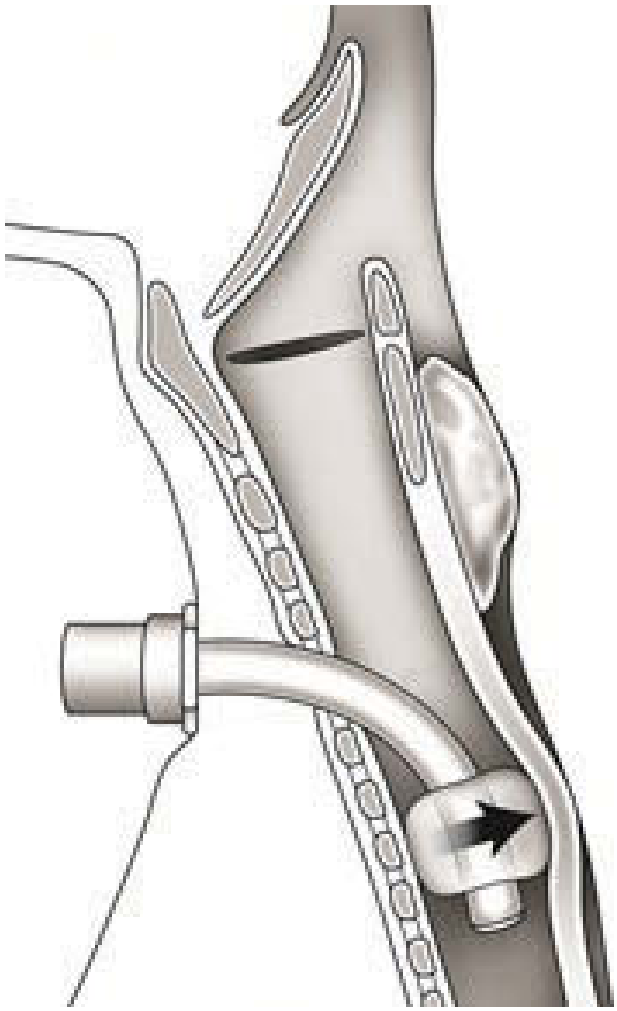

Figure 56.1 A tracheostomy tube can have an adverse effect on swallowing by reducing laryngeal elevation and also by oesophageal compression through direct transmission of cuff pressure.

SURGERY FOR CHRONIC ASPIRATION

Patients with palatal incompetence suffering nasal reflux or escape may benefit from prosthetic appliances to elevate the soft palate, or velopharyngeal flap techniques may be considered.[15]

In cases of dysphagia and aspiration due to parapharyngeal or retropharyngeal masses, then surgical removal of these is likely to be helpful.

It is well recognized that the trans-oral laser approach to removing even small tumours on the posterior pharyngeal wall may result in severe dysphagia and aspiration,[16] even in the younger patient. This is thought to be due to disruption or damage to the pharyngeal plexus. Careful thought should also be given to external surgical approaches to the pharynx and upper oesophagus in the older patient. These patients have minimal swallowing reserve and surgical scarring contributing to tethering of the larynx or pharynx, or damage to the pharyngeal plexus may adversely affect the safety of swallowing.

Sometimes osteophytes from the cervical spine will be seen to overhang the laryngeal inlet and act as a 'ski-slope' for food and secretions in to the airway (**Figure 56.2**). The trans-oral, trans-pharyngeal approach to these will certainly risk exacerbating the swallowing problem. An external approach to the anterior cervical spine, with

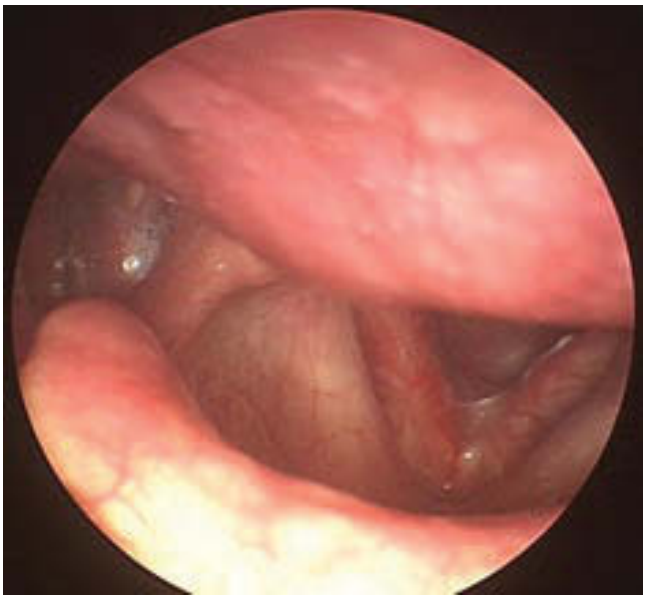

Figure 56.2 Osteophyte from cervical spine overhangs the laryngeal inlet and can be associated with secretions dripping into the airway.

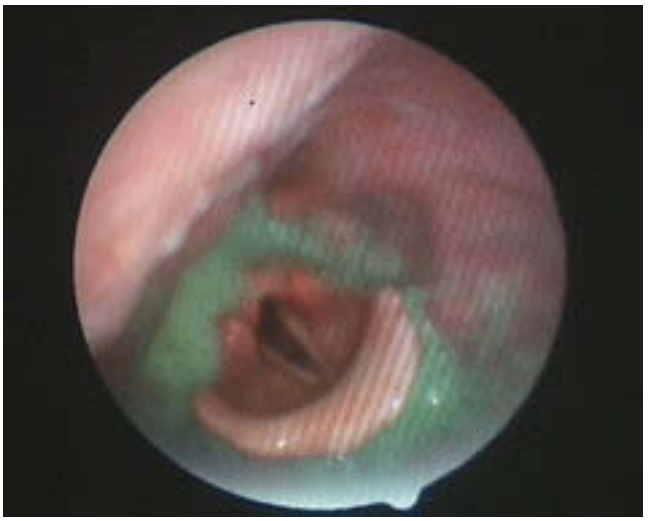

Figure 56.3 Fibre endoscopic view of larynx in a patient who has aspiration (milk with green dye during FEES study).

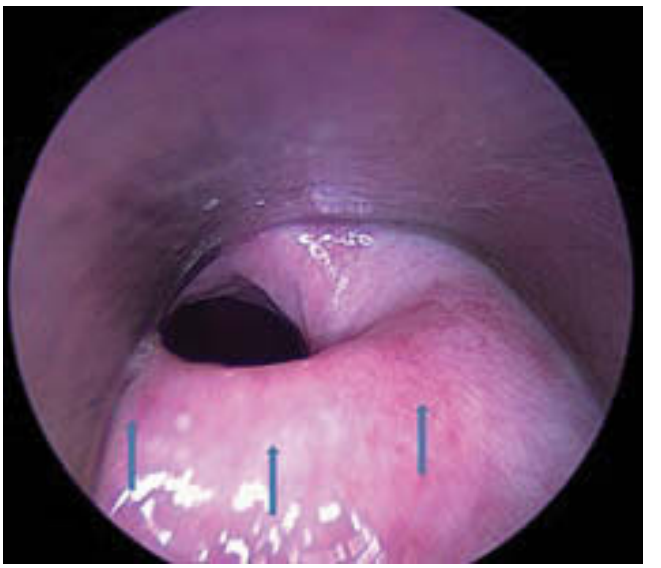

Figure 56.4 View of cricopharyngeus through a laryngoscope. Botulinum toxin is injected in the three positions (arrows) to produce the effects of a 'temporary myotomy'.

lateral retraction of the larynx and pharynx, is a viable option but may affect swallowing, for the same reasons mentioned earlier in this chapter, and there is potential for injury to the recurrent laryngeal nerve. Sometimes a laryngeal suspension procedure will elevate the larynx away from such an osteophyte and not risk the swallow further.

SURGERY TO THE CRICOPHARYNGEAL SPHINCTER

If flexible nasendoscopy demonstrates pooling of secretions in the hypopharyx (**Figure 56.3**), then based on the medical history and videofluoroscopic imaging it is possible to determine whether this is due to weakness of the pharyngeal musculature, a hypertonic or discoordinated cricopharyngeal sphincter, or both.

In these circumstances it is logical to think about an upper oesophageal myotomy. One cannot always be confident of the results of an external approach myotomy and for this reason the authors prefer a trial of a 'medical myotomy' using botulinum toxin.[17] A total of 80–120 units of botulinum toxin A is administered into cricopharyngeus in three separate injections, dividing the total dose. A short general anaesthesia and direct visualization of this muscle, using a laryngoscope, allows one central and two postero-lateral injections to be placed accurately (**Figure 56.4**). If this treatment is successful it can either be repeated or be followed by an endoscopic CO2 laser myotomy (**Figure 56.5**).[18] Very rarely is an external approach myotomy required.

LARYNGEAL INCOMPETENCE

The airway has several levels of protection against aspiration. During a swallow the larynx moves up and forwards to lie under the tongue base, the epiglottis moves to lie above the laryngeal inlet and the true and false cords adduct. If there are residual secretions in the hypopharynx, aspiration can still take place even if the larynx is functioning normally. Even though the larynx elevates during a swallow, as it descends to its resting position retained secretions can enter the airway. Usually this will produce a cough, but this may not be the case in a neurologically impaired patient. In addition, when the larynx has been exposed to chronically retained secretions there is associated oedema of the laryngeal mucosa and diminished supraglottic sensation.

More commonly the cause of laryngeal incompetence is damage to a vagal nerve, high in the neck, which affects both motor and sensory function of the unilateral larynx as well as the associated pharyngeal musculature.

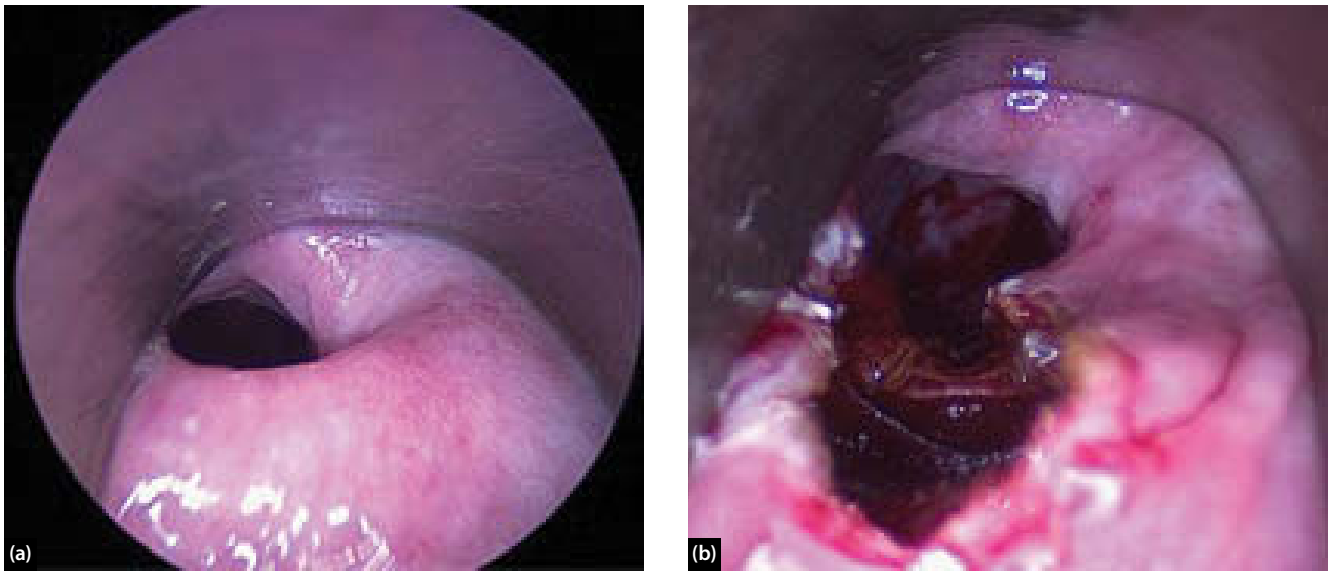

Figure 56.5 Result of endoscopic CO2 laser cricopharyngeal myotomy (right).

Cerebrovascular events, especially if involving the brainstem, and progressive muscle wasting conditions can also lead to impaired laryngeal and pharyngeal competence. A plethora of approaches has been described to deal with this particular problem; the sheer variety, and the absence of large trials, would suggest inconsistent results.

Bilateral vocal fold medialization techniques have been described to deal with this problem. These can consist of injections lateral to the thyroarytenoid muscle. Laryngeal injections can be carried out under local or general anesthesia and most are temporary (see Chapter 68, Movement disorders of the larynx). They are ideally suited for conditions where there is likely to be a recovery of laryngopharyngeal function within a few weeks, or as a test of medialization suitability prior to medialization thyroplasty procedures that are described as permanent. Thyroplasty implants include Gore-Tex ribbon, titanium, hydroxylapatite and silicon. Bilateral medialization thyroplasties were first described for vocal cord bowing[19] as seen with presbyphonia. In these circumstances the posterior edge of the implant needs to sit anterior to the vocal process of the arytenoid so that it does not interfere with normal abduction of the cords. However, bilateral medialization for aspiration requires adduction of the entire vocal cord.[20] The technique works in carefully selected cases of mild aspiration[21] as it does not prevent all aspiration and risks patients requiring a tracheostomy.

Unilateral vocal fold medialization or arytenoid adduction[22] techniques in combination with cricopharyngeal myotomy are described for cases of vagal nerve injury leading to aspiration. In some cases of high vagal injury there is associated hypopharyngeal dilatation leading to excessive pooling of secretions in the pyriform. Denker originally devised a technique for excising the redundant pharyngeal mucosa on the affected side, through an external approach, which others have modified with the use of plication sutures or a stapling device.[23] With these 'hypopharyngeal pharyngoplasty' procedures it is usually necessary to perform a cricopharyngeal myotomy and cord medialization at the same time.

GLOTTIC AND SUPRAGLOTTIC LARYNGEAL CLOSURE

The first glottic closure procedure, performed through a median laryngofissure, was described by Montgomery in 1975[24] and involved stripping the vocal cord mucosa on both sides and suturing the cords together to encourage fibrous union. As an alternative to damaging the vocal cords, a two-layered closure of the supraglottis (**Figure 56.6**) was devised via a pharyngotomy approach.[25] This was later modified by Remacle et al.[26]

The problems with these two approaches are that they run a high risk of breakdown and, as the larynx is closed, the patient is tracheostomy dependent and has no voice. Also these procedures are not easily reversible. In 1975 Biller et al.[27] described a two-layer, vertical supraglottic closure, with a small opening at the tip of the epiglottis (**Figure 56.7**). The procedure was designed to prevent aspiration in total glossectomy patients. Some retained the

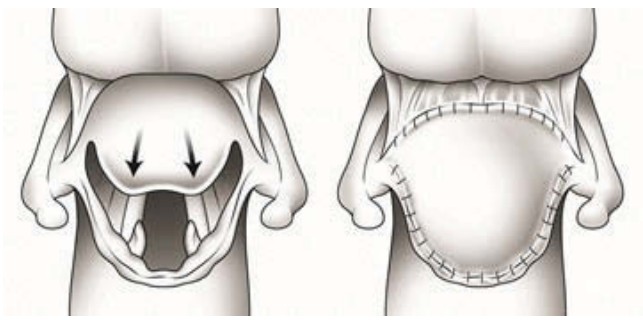

Figure 56.6 Horizontal closure of the supraglottic larynx via a lateral pharyngotomy approach.

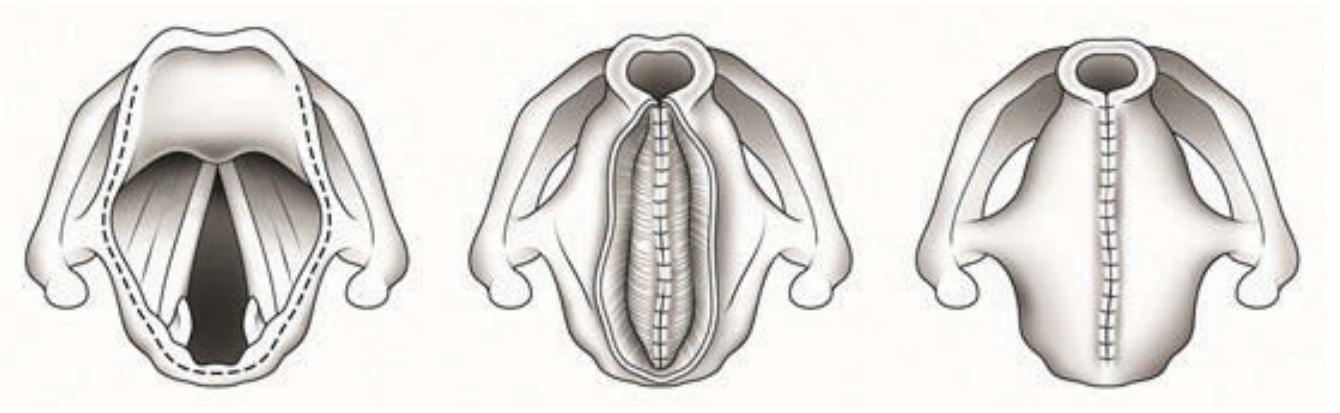

Figure 56.7 Biller supraglottic laryngoplasty for treating chronic aspiration in total glossectomy patients.

ability to speak and others could commence oral intake but retained a tracheostomy tube.[28]

LARYNGEAL PROSTHESES

A translaryngeal, closed stent is one means of preventing aspiration and can be placed endoscopically and held in place with trans-cervical sutures.[29] The theoretical advantage is that the stent can be removed if the patient recovers a safe swallow. Unfortunately these stents cause scarring at the level of the glottis, are uncomfortable and do not provide a reliable seal to secretions.[30] With advances in biointegratable materials and the work on implantable larynges[31] there is hope for prostheses that allow voicing, without aspiration, but the patient may still need a tracheostomy.

OESOPHAGEAL MOTILITY DISORDERS

Oesophageal motility disorders can lead to retained secretions in the hypopharynx and risk aspiration. They result from either primary diseases of the musculature or from an imbalance between excitatory and inhibitory innervations. Historically the diagnosis has been based on VF but high-resolution manometry with oesophageal pressure topography has become the current gold standard.

Abnormalities of oesophageal function are common in patients with gastro-oesophageal reflux disease (GORD).[32] Mild cases of dysmotility can be managed by suppressing gastric reflux through the use of proton pump inhibitors, prokinetic antibiotics (macrolides) or prokinetic drugs (domperidone). In severe cases, such as spasm or hypertensive peristalsis, medical treatment with nitrates and calcium channel blockers may prove effective. Endoscopic dilatations and Botox injections may help with more localized problems such as achalasia (lower oesophageal sphincter) or cricopharyngeal spasm (upper oesophageal sphincter). A permanent solution in these patients includes a myotomy.

Secondary motility disorders may be related to neurological or connective tissue diseases, as well as diabetes and rarer disorders such as amyloidosis, Sjögren's syndrome and eosinophilic oesophagitis.

PHARYNGEAL POUCH

A pharyngeal pouch (Zenker's diverticulum) is a posterior pulsion diverticulum occurring, in a natural weakness (Killian's dehiscence), between the fibres of thyropharyngeus and cricopharyngeus. They are associated with an oesophageal motility disorder in the vast majority of cases. The symptomatic patient complains of dysphagia, regurgitation of food, coughing, aspiration or repeated chest infections. Treatment is indicated when symptoms impact on quality of life or pose a risk to the patient's health.

Endoscopic techniques transect the diverticulo-oesophageal wall so that material does not collect in the pouch. This transection also divides cricopharyngeus (**Figure 56.8**) and some upper oesophageal muscle fibres, and quite neatly performs a synchronous myotomy (**Figure 56.9**). Division of this dividing wall has evolved from using electrocoagulation, the CO_2 laser and more recently endoscopic stapling devices.[33] The endoscopic approach is not always feasible if there is poor access

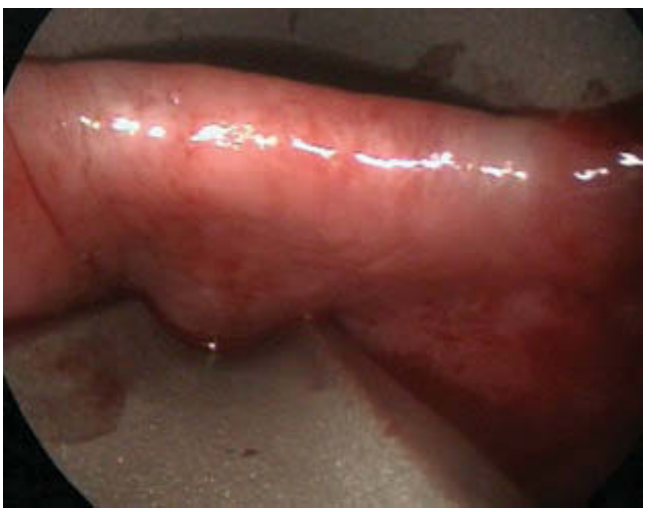

Figure 56.8 Pharyngeal pouch party wall.

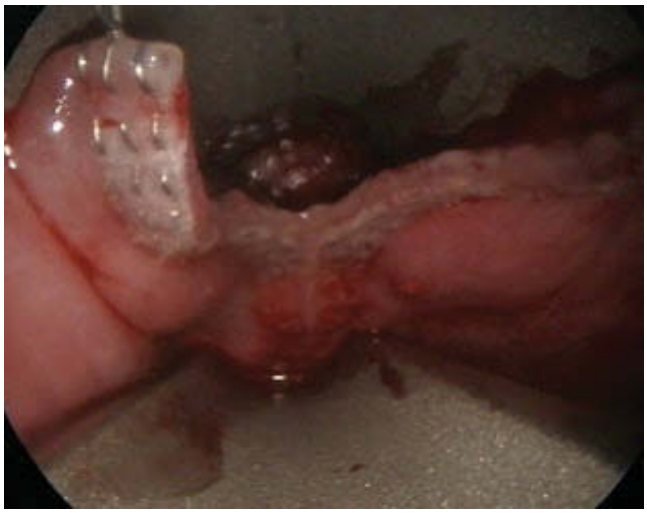

Figure 56.9 Pharyngeal pouch party wall divided.

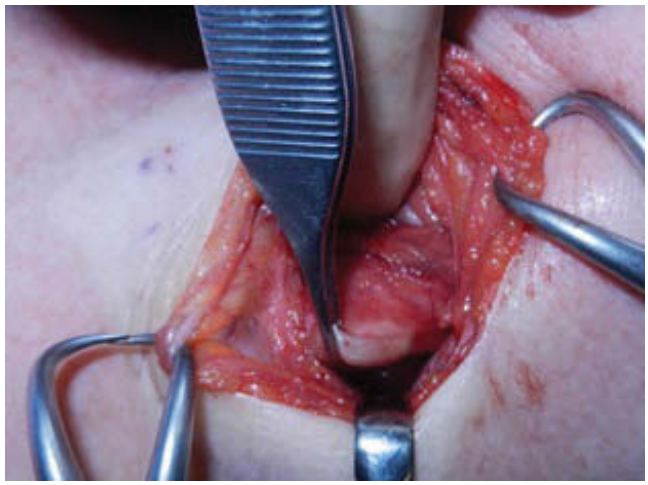

Figure 56.10 Open pharyngeal pouch excision.

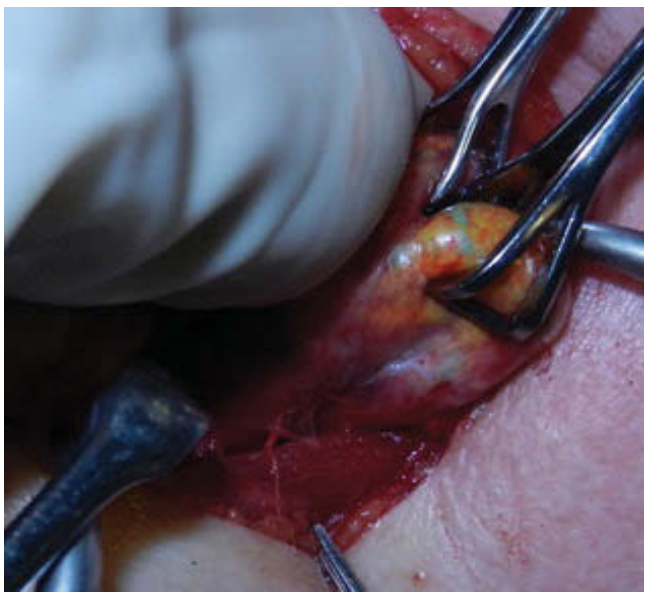

Figure 56.11 Proflavine impregnanted ribbon gauze visible in pharyngeal pouch.

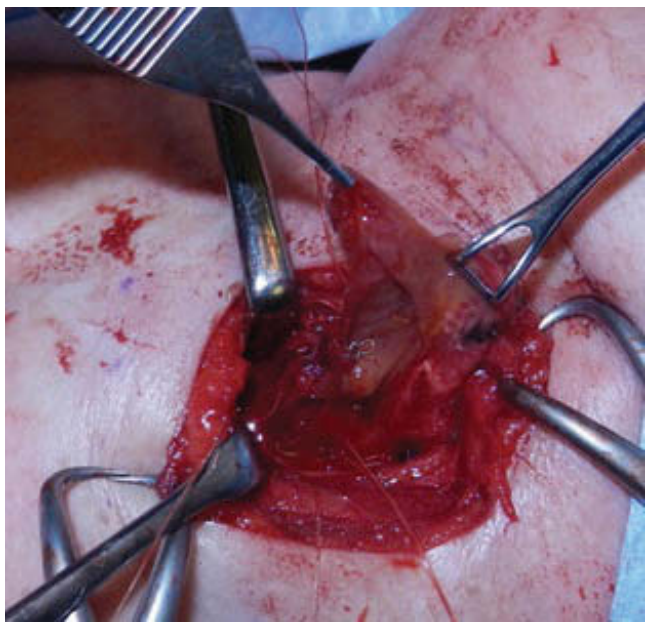

Figure 56.12 Mucosal edge of open pharynx and oesophagus with pouch excised.

and it is not always suitable for very small or very large pouches, and there is still a small incidence of post-operative leaks with the risk of mediastinitis.[34] In some cases it is necessary to perform an external approach diverticulectomy (**Figures 56.10–56.12**) combined with a cricopharyngeal myotomy. This does, however, mean a longer hospital stay with increased morbidity (see Chapter 52, Cricopharyngeal dysphagia).

RADIOTHERAPY-RELATED DYSPHAGIA AND ASPIRATION

Radiotherapy to the head and neck is responsible for both early and late changes to the irradiated site. The effects of radiotherapy can vary between individuals even if the dosing is identical. In general the degree of radiotherapy damage depends on: total dose; adjuvant chemotherapy; the extent of the radiotherapy fields at the primary site; and whether the neck has also been treated.

Early radiotherapy therapy changes include mucositis, erythema and pain but also oedematous thickening of soft tissues, weakness of muscles altered taste, altered sensation and reduced oral secretions. Late changes (beyond 6 months) include tissue fibrosis, damage to the blood supply, neuropathic changes, reduced contraction of muscles and joint mobility restriction. The irradiated pharynx will be poorer at clearing secretions and the larynx, if irradiated, may demonstrate poor closure and elevation. In patients receiving radiotherapy for hypopharyngeal or post-cricoid tumours, the scarring and stricture formation may continue for 10 to 20 years after exposure and aspiration may be a very late presentation.

Treatment of post-radiotherapy-related dysphagia and aspiration includes compensatory manoeuvres, dietary

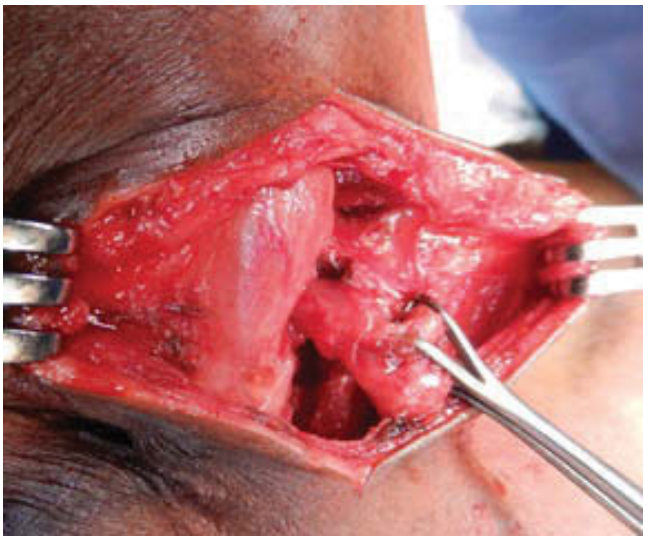

Figure 56.13 Transverse colon transposition in a patient with caustic injury to the pharynx, oesophagus and gastroduodenal areas. Hypopharynx visualized, scarred neck from previous surgery for caustic pharyngeal and oesophageal injury.

modifications and other forms of nutrition. Surgical options are often limited to serial dilatations or ultimately a laryngectomy or laryngopharyngectomy with free flap reconstruction. The authors have used lateral pharyngeal augmentation techniques, with rotational or free myocutaneous or bowel flaps, in cases of hypopharyngeal strictures following caustic ingestion (**Figures 56.13–56.16**), in whom results are more favourable, but the results in radiotherapy patients have been poor.

New radiotherapy techniques, such as intensity-modulated radiotherapy (IMRT), can minimize exposure and damage to structures related to swallowing and the salivary glands and are likely to reduce the incidence of these complications.

LARYNGOTRACHEAL SEPARATION

Laryngotracheal separation[35] is described as a simple procedure that allows protection of the airway, while preserving the swallow. The patient's lower airway opens as stoma in the neck and the trachea just below the subglottis is closed as a 'blind-ending' (**Figure 56.17**). As it is reversible it has the potential for restoring voice when the patient recovers. It is however, associated with a high incidence of complications (40%) that include wound breakdown and fistulae, and also airway stenosis at the subsequent tracheal anastomosis; some of the patients go on to require a long-term tracheostomy or laryngectomy.[36]

Tracheo-oesophageal diversion is a modification of the Lindeman procedure described above. The proximal tracheal segment is anastamosed in an end-to-side fashion to an opening in the anterior oesophagus thus eliminating the 'sump' of secretions that results with the former technique. The modification does add to the potential for complications at the primary procedure and when reversed. Both of these procedures make it difficult to be confident

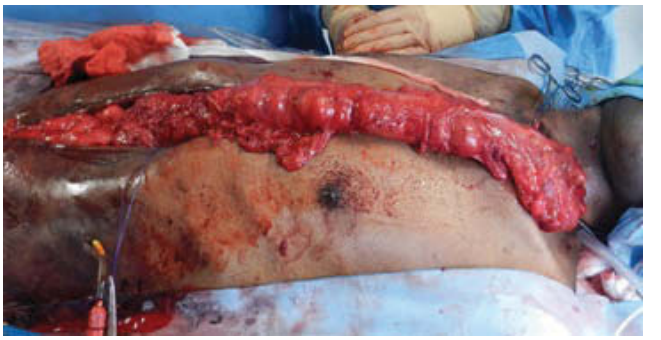

Figure 56.14 Transverse colon mobilized in a heavily scarred abdomen.

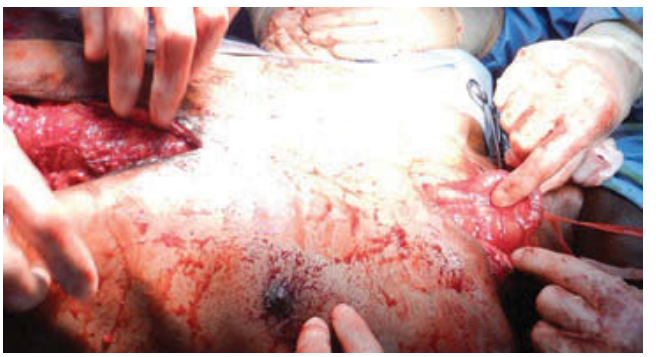

Figure 56.15 Transverse colon mediastinal transposition.

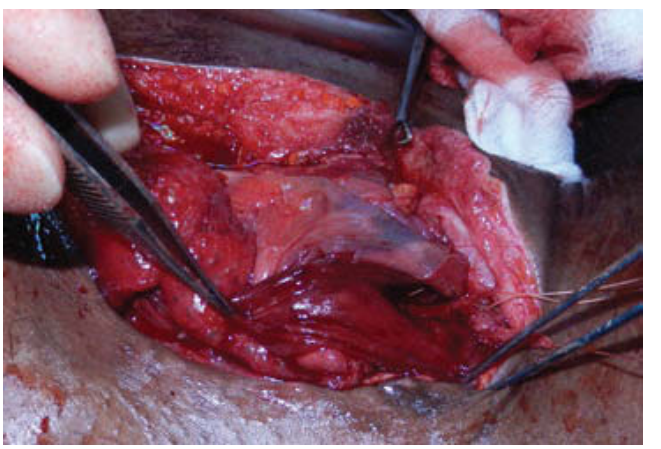

Figure 56.16 Pharyngo colonic anastomosis.

of adequate recovery of swallowing function to commit to a reversal, as evidenced by the number of patients requiring subsequent tracheostomies and laryngectomies.[36]

LARYNGEAL AND LARYNGOHYOID SEPARATION

In severe cases of aspiration where there is reduced laryngeal elevation, excessive pooling of hypopharyngeal secretions and reduced laryngeal sensation, or severely discoordinated swallowing, the aspiration poses a significant risk to life. If there is also limited likelihood of recovery of swallow function, yet life expectancy is still

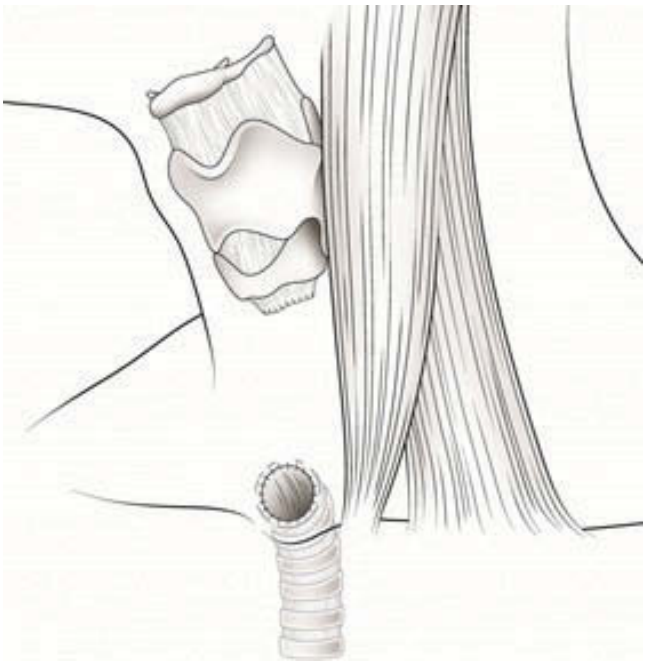

Figure 56.17 Laryngotracheal separation procedure. The airway is closed below the subglottis and the distal trachea is brought out to the skin surface as a stoma.

reasonable, then the safest option is to consider a narrow-field laryngectomy.

There are, however, some intermediate measures to consider before taking such a drastic step. Laryngeal suspension to the hyoid bone is well documented[37] but the results are not always reliable. Part of the problem is that the degree of suspension achieved is fairly limited and often less than 1 cm. The authors have developed an 'enhanced laryngeal suspension' procedure where the thyroid cartilage is removed starting a few millimetres above the level of the glottis, the base of the superior horn of this cartilage is also resected and a more significant thyrohyoid approximation is achieved using braided monofilament sutures. As the sutures in the thyroid cartilage are placed postero-laterally and those in the hyoid near the midline, anterior transposition of the thyroid cartilage is achieved. This technique should be performed synchronously with a cricopharyngeal myotomy and can be combined with a medialization thyroplasty (**Figure 56.18**).

Hans Mahieu[38] performs a standard laryngeal suspension but also suspends the thyrohyoid complex to the mandible (**Figure 56.19**) and includes an upper oesophageal sphincter myotomy. This elevates the larynx away from hypopharyngeal secretions but also pulls open the upper oesophageal inlet.

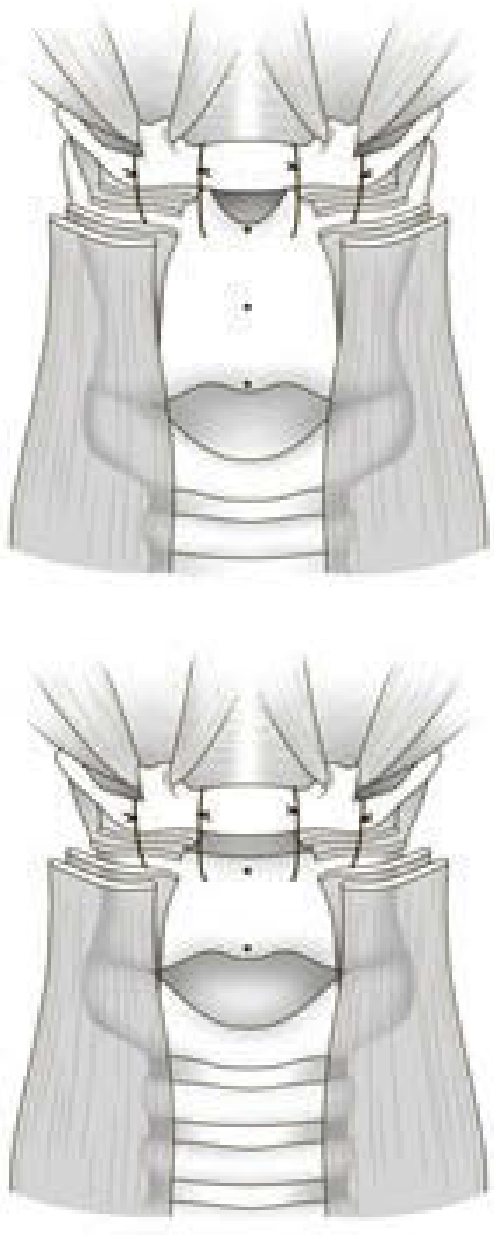

Figure 56.18 (a) a standard laryngeal suspension. (b) an enhanced laryngeal suspension. The thyroid cartilage is excised, from within its perichondrium, above a line representing the level of the glottis (midpoint dot on (a)). The base of the superior horn of the thyroid often needs to be divided to allow successful thyrohyoid approximation.

LARYNGECTOMY

A narrow-field laryngectomy removes the laryngeal skeleton but spares the hyoid, the strap muscles and hypopharyngeal mucosa allowing for a multiple layer closure with reduced incidence of a fistula. Preservation of pharyngeal mucosa also means that pharyngeal closure could be achieved using a linear stapling device[39] and feeding commenced within 5–7 days.

DISCUSSION

The ideal surgical procedure for chronic aspiration would be simple, associated with few complications, allow speech and swallowing, and be easily reversible without long-term sequelae. The majority of patients with a

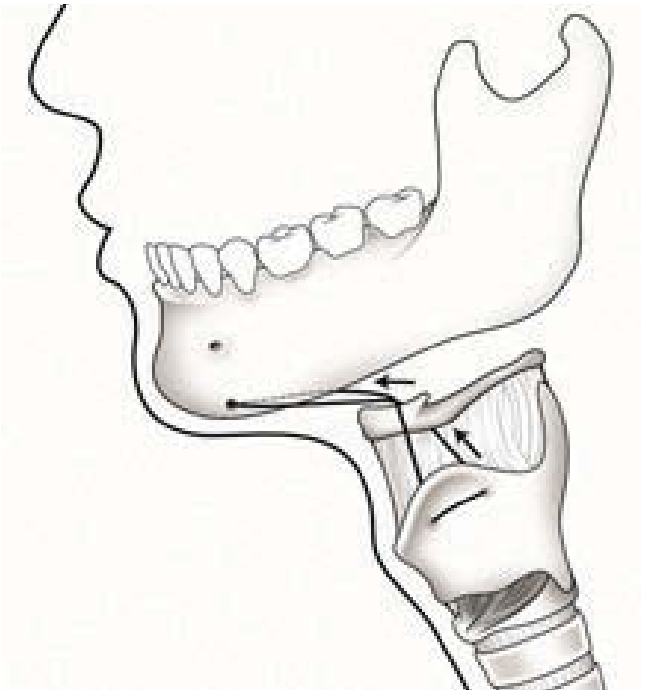

Figure 56.19 Thyrohyoid complex is suspended to mandible.

reversible neurological deficit tend to show recovery within a few months and it is the practice in most units to manage these patients with tracheostomies and feeding tubes even though this may be far from ideal. There are therefore very few indications for reversible procedures. Dysphagia with mild aspiration due to dysfunction of cricopharyngeus, weakness of the hemilarynx or reduced pharyngeal constrictor activity can usually be managed with a cricopharyngeal myotomy, vocal cord medialization with or without excision of the redundant pharyngeal mucosa. Laryngeal or laryngohyoid suspension may be considered in more severe cases.

The difficult decision is in those patients who are not going to recover a safe swallow or who are suffering with either a neurological condition that is progressive, or severe scarring and contracture related to radiotherapy treatment. Supportive procedures described above may be helpful for a period but there will come a time when a laryngectomy may become the procedure of choice. It provides a definitive separation of the respiratory and digestive tracts. Feeding tubes and tracheostomies are avoided and depending on residual dexterity and neurological function surgical voice restoration may be possible.

KEY POINTS

- Swallow disturbances may arise from deranged function in the oral cavity through to the oesophagus.
- Dysphagia patients should be assessed in the MDT clinic.
- Directed dysphagia history will identify the likeliest cause of dysphagia.
- Qualitative questionnaires can help chart management response.
- Swallow therapist instruments for swallow including FEES VFS are necessary before trialling intervention.
- Temporary procedures should be trialled before embarking on irreversible surgical correction of aspiration.
- The larynx is the prime organ for airway protection whilst the pharynx is actively involved in deglutition.

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CHAPTER 57

TEMPOROMANDIBULAR JOINT DISORDERS

Andrew J. Sidebottom

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SEARCH STRATEGY

Data in this chapter are based on a PubMed search using the keywords: temporomandibular joint, temporomandibular disorder, TMJ pain, myofascial pain, rheumatoid arthritis, arthroscopy, arthrocentesis and joint replacement.

INTRODUCTION

Temporomandibular joint (TMJ) problems are a common cause of morbidity with around 30% of the population complaining of problems related to the joint at some stage during their life. Approximately 10% of the population has one or more TMJ symptom or sign at any one time. Differential diagnosis can be confusing and patients are often considered to have 'earache' and referred for ear, nose and throat (ENT) advice. This chapter will aim to provide guidance in the differential diagnosis and primary management of TMJ disorders, with advice when onward referral for subspecialist surgical advice is appropriate.

The most common form of TMJ disorder has various names, including TMJ pain dysfunction, myofascial pain dysfunction and TMJ dysfunction syndrome. Internationally the term temporomandibular disorder (TMD) has been largely introduced from the research and diagnostic criteria. This is a group of disorders of the joint and related masticatory muscles and is best defined as a spectrum from internal derangement (disc-related disorder) to masticatory myofascial pain (purely muscle disorder). The majority of this chapter will deal with this spectrum but will include the other less common disorders affecting the joint.

EPIDEMIOLOGY OF TMJ DISEASE

TMJ disorders present in all age groups, but in the under-40s there is little degenerative disease, unless there is a history of significant trauma or joint surgery. In the over-40s there is increasing evidence of remodelling of the joint (wear and tear or osteoarthrosis) and ultimately degenerative disease (osteoarthritis when associated with pain and inflammation), although this may not be the cause of the patient's symptoms. Symptoms however, present more commonly in the under-40s.

In youths (14–30 years), acute restriction of opening is generally due to a reduction in lubrication within the joint – called anchored disc phenomenon[1] – and this can be dealt with effectively by arthrocentesis (joint washout under pressure; see below). Additionally, acute muscle spasm secondary to clenching or grinding (particularly around the time of examinations or other times of stress) is common in this age group. This problem can also affect older age groups at times of stress as the balance of wear

and tear to repair is tilted towards the former by raised adrenaline levels causing increased muscle spasm, with induction of myofascial type symptoms and consequent compression of the joint.

Women seem to be affected more commonly than men with various ratios from 2:1 to 10:1 being reported.[2] The rationale behind this may be a variance in oestrogen joint receptors although the correlation of this is not fully clear, with raised free radicals also being found in joint aspirates of affected individuals.

Predisposing factors include previous trauma to the joint (macro-trauma) including previous open joint surgery, a history of a clicking joint (present in up to 30% of the population) and a history of clenching in particular, but also grinding (nocturnal bruxism), which causes recurrent microtrauma. There is no conclusive evidence for the role of occlusal/dental factors in induction of disease; indeed, the American Association of Orthodontists devoted significant research into this area in the late 1980s to show that orthodontic management did not induce or reduce the incidence of TMJ disorder or clicking during or after orthodontic treatment. Subsequent Cochrane studies[3] have shown no benefit for occlusal modification in the management of TMJ disorders, as much of the literature on TMD are case series, not randomized studies.

HISTORY OF TMJ DISEASE

The primary symptoms to be elicited from the history (**Box 57.1**) are discussed below.

Pain

Pain from TMD may be from the joint itself (TMJ pain) or in the related muscles of mastication (myofascial pain). The history and examination should distinguish these two prior to definitive management, although initial care is the same for both. Often both are interlinked, giving a spectrum of disease from joint pain at one end to muscle pain at the other. Pain should be recorded using a reproducible pain score, such as a 10 cm analogue scale such that outcomes can be assessed.

Pain localized in front of the tragus of the ear, which can be pointed to with the finger, is likely to be TMJ pain. It is often made worse by function (eating and yawning), and may radiate to surrounding structures. Biting on a tongue spatula on the side of the pain induces the pain in the joint, helping to confirm the diagnosis.

BOX 57.1 Symptoms to be determined from clinical history

1. Pain
2. Joint noises
3. Locking
4. Restriction of opening
5. Disturbance of the bite
6. Alteration in facial appearance
7. Other joint disorders, particularly rheumatological and hypermobility

Myofascial pain is often less well defined with complaints of 'numbness' or aching on the side of the face, which is poorly localized but often in the region of the ramus of the mandible or lateral cheek below the zygomatic process or into the temple. This tends to be worse in the mornings, due to clenching or grinding the teeth at night (a habit that can sometimes be confirmed by the patient's partner), or after particularly 'stressful' situations (e.g. a long drive through heavy traffic or around exam times). Occasionally temporalis pain may be described as headache.

Joint noises

Clicking or cracking of the joint are common. Clicking is related to anteromedial displacement of the disc (ADD) of the TMJ repositioning itself over the joint and predisposes to joint disease (see under 'Internal derangement' below). Click alone does not warrant any treatment other than reassurance that it will reduce with time and does not indicate or lead to 'arthritis of the joint'. Cracking or crepitus again does not warrant treatment but suggests 'scarring' or degeneration within or around the joint. Without associated symptoms the patient can be reassured, although occasionally it can be a presentation of arthritic conditions.

Locking

Locking is the inability to either fully open or fully close the joint. Inability to fully open the joint (confusingly called closed lock) will often be overcome following massage, with a click or crunch restoring full opening. This was considered to be due to anteromedial disc displacement with reduction (ADDR), although it may be due to acute muscle spasm of the lateral pterygoid muscle, which attaches to the anterior portion of the disc, or any of the other muscles of mastication (secondary to myofascial spasm). It may also be due to alteration in the lubrication of the joint (anchored disc phenomenon). Inability to fully close over a period of time (open lock) is usually due to a joint effusion (synovial fluid) or blood (haemarthrosis). Both may be secondary to trauma although the former may also be secondary to the acute synovitis seen in rheumatoid diseases. The frequency of locking should be recorded.

Restriction of opening

Normal range of mouth opening for an adult is above 35 mm inter-incisal distance (with upper and lower dentures in if present). An opening greater than 55 mm suggests hypermobility.

Muscle spasm and disc displacement can both cause restriction, as can ankylosis of the joint, trauma or the spasm associated with cervicofacial infection. Opening less than 25 mm in a young adult without associated systemic illness suggests anchored disc phenomenon, due to loss of joint lubrication. This should be managed urgently

by a maxillofacial specialist with an interest in TMD who will consider early arthrocentesis which is usually curative. Significant delay may lead to a permanent restriction (**Figure 57.1**).

Disturbance of the bite

Collapse of the joint with reduction in height of the ramus will cause a premature contact on the side of the collapse. There may be associated centreline deviation of the chin or teeth towards the side of collapse. If both sides collapse the chin point will move backwards (class 2 deformity) with bilateral loss of ramus height and an anterior open bite (inability of the front teeth to bite together).

Alteration in facial appearance

Collapse of the joint may cause retrusion of the chin if bilateral, or rotation of the chin centreline towards the side of collapse. In addition there will be loss of definition of the angle of the mandible due to loss of ramus height (**Figure 57.2**). The opposite features occur where there is joint overgrowth with centreline deviation towards the opposite side and lengthening of the ramus with possible open bite on the affected side.

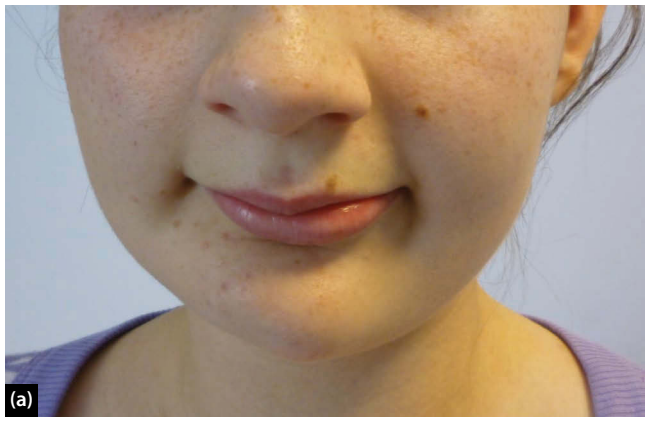
Other joint disorders

The TMJ can be affected by rheumatoid joint diseases or hypermobility.[4] Rheumatoid disease often presents with pain and ultimately can lead to joint collapse with a disturbance in the way the teeth bite together (malocclusion) or ankylosis. Ankylosing spondylitis may lead to joint ankylosis with pain and restriction of opening. Psoriatic arthropathy also may cause pain, restriction, ankylosis and occasionally joint collapse.

Hypermobility can lead to joint dislocation. This occurs when the condyle of the mandible is displaced anterior and superior to the articular eminence of the temporal bone. It tends to occur in two age groups – young adults with generally hypermobile joints and the elderly who have loose ligaments and overclosure of the jaw due to lack of teeth. The frequency of dislocations should be recorded. Often patients may complain of 'dislocation' when in fact they are describing a click or locking.

CLINICAL EXAMINATION

The aim of clinical examination is to determine the sites of tenderness and the degree of disorder present. The examination comprises the steps shown in **Box 57.2**.



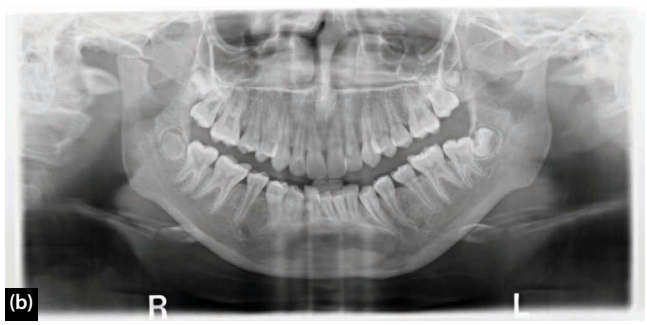
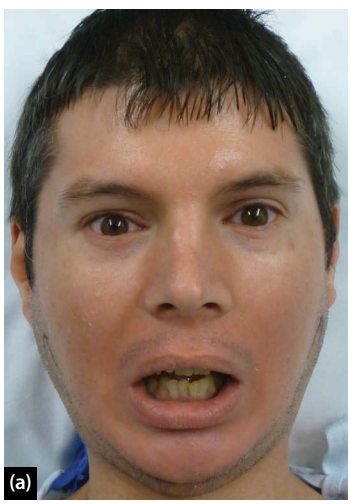


Figure 57.2 (a) A young woman with juvenile arthritis of the TMJ, demonstrating undergrowth on right side. **(b)** The OPG of the same patient showing condylar under-development on the right side.



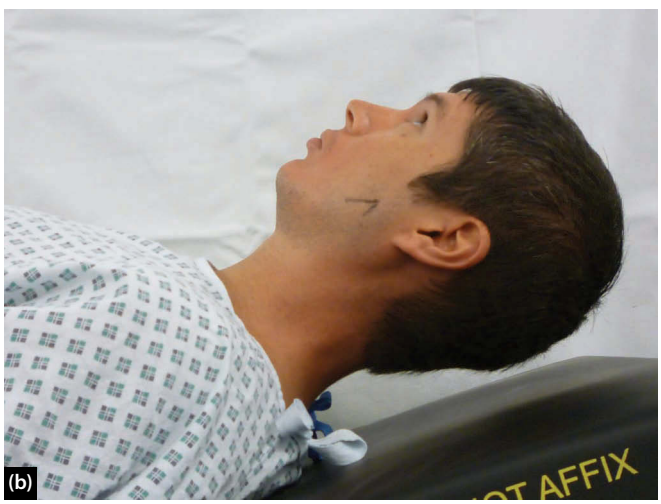


Figure 57.1 (a) Limited mouth opening in a young man with psoriatic arthropathy. **(b)** Fixed neck flexion in the same patient due to pseudo ankylosing spondylitis.

BOX 57.2 Clinical examination of the TMJ

- Palpation of the joint for tenderness and noises/crepitus laterally and posteriorly with the mouth both closed and open
- Palpation of the masseter muscles for tenderness and areas of muscle tightness
- Palpation of the temporalis muscles for tenderness and areas of muscle tightness
- Use of a tongue spatula to bite between the teeth on each side
- Measurement of inter-incisal mouth opening in millimetres
- Observation of the opening path of the mandible in relation to the maxillary centreline
- Interdigitation of the teeth (dental occlusion)

Palpation of the joint

The TMJ is palpated just in front of the tragus of the ear. Movement consists of rotation in the lower joint space and glide from the upper joint space over the articular eminence at the base of the zygomatic arch. Tenderness may be elicited over the lateral aspect of the joint while stationary or in motion. The posterior aspect of the joint can only really be felt in wide opening by palpating between the back of the joint and the tragal cartilage or with a finger in the external auditory canal. Tenderness over a joint indicates inflammation in the joint related structures of capsule, synovium and bone.

Noises may be palpated and heard such as a click or crepitus (crunching). Due to the close relation of the joint to the ear, the patient may complain of noises that either are intermittent or cannot be palpated or heard by the examiner. Assume the noise is present if the patient complains of it. Tinnitus is not generally a symptom of TMD.

Palpation of the masseter and temporalis

The masseter muscles lie over the vertical ramus of the mandible up to the base of the zygomatic arch. The temporalis lies above the zygomatic arch, extending behind and above the ear and onto the forehead below the hairline. Tenderness in a muscle during clenching or the palpation of tight bands of muscle indicates myofascial spasm and pain.

Headaches may be a symptom of TMJ disorder when there is associated muscle or joint tenderness, but alone are not indicative of TMJ problems. They may also be associated with stress-related disorders.

Use of a tongue spatula

It is relatively difficult and impractical to determine areas of tenderness in the other muscles of mastication and the author does not feel this is necessary in non-specialist practice. Placing a tongue spatula between the teeth and asking the patient to bite on it will elicit pain in the joint on the ipsilateral side or pain in the lateral pterygoid on the contralateral side, and provides a useful indirect palpation of the muscle.

Measurement of inter-incisal opening

The distance between the upper and lower incisors during maximal mouth opening gives a reliable and reproducible measure of loss of function and outcome. Around 97% of the population has an opening of greater than 35 mm and this provides a useful distance to aim for as a treatment outcome. Some patients with an opening greater than this will have subjective restriction and others with an opening less than this will be normal. Improvement in opening following treatment gives a good measure of outcome.

Observation of opening path

Mouth opening tends to deviate towards the side of pathology. The early phase of opening is a rotation of the condyle of the mandible against the disc in the lower joint space. From 20–25 mm, opening continues with glide between the disc-condyle complex and the glenoid fossa of the temporal bone in the upper joint space. This latter movement causes the joint to move away from the side of the gliding. As much of the joint pathology causing restriction is related to upper joint space problems, muscle spasm restricting disc movement or muscle or joint pain restricting movement, the loss of glide is the most common outcome and therefore the 'normal' joint glides causing the jaw centreline to deviate towards the diseased side. Looking for this particular clinical sign aids confirmation of the side and site of the problem.

Interdigitation of the teeth (dental occlusion)

The way the teeth bite together can be altered by joint collapse. If one joint collapses the fulcrum on that side moves superiorly, causing the posterior teeth to meet prematurely on that side and the centreline to deviate towards that side. If both sides collapse, the front teeth will not meet (anterior open bite) when the patient reports they previously did (**Figure 57.3**).

Conversely, if there is an effusion (inflammatory fluid in the joint) or haemarthrosis (blood in the joint) the joint space increases, lowering the fulcrum, preventing the posterior teeth on the side of the effusion from meeting. Minor variances in the occlusion are usually irrelevant.

INVESTIGATIONS

Plain radiographs form the mainstay of initial examination of the TMJ, although they have little diagnostic value as they only show a section of the joint surface and show nothing of the soft tissues associated with the joint. Other pathologies should be excluded (including dental pain, sinus problems, trigeminal neuralgia etc.) from the history and examination, and often an orthopantomogram (OPG) radiograph is taken to exclude possible

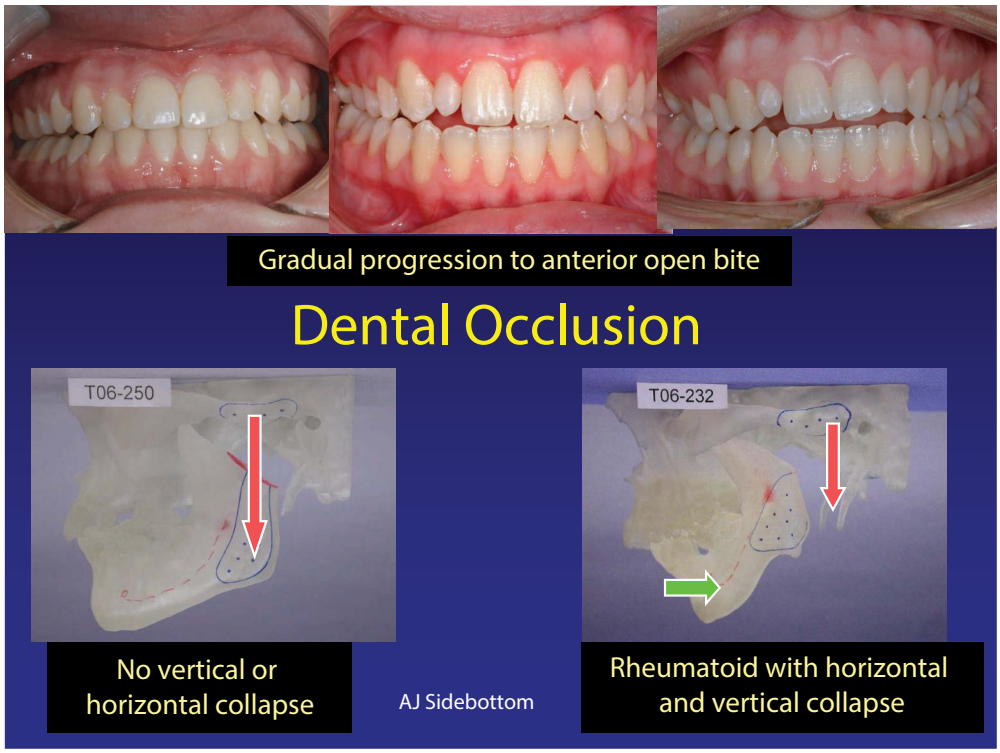


Figure 57.3 These pictures illustrate the development of anterior open bite and ramal collapse in a patient with bilateral temporomandibular joint collapse. The accompanying models of the facial skeleton demonstrate the joint collapse.

dental causes. Transpharyngeal and transcranial views may be requested, as may open and closed views, but they add little to a thorough clinical examination and an OPG showing both TMJs.

Further investigations, where indicated, include an isotope bone scan if hyper or hypoplasia of the condyle is suspected. CT scanning of the joint shows the bony structures well and three-dimensional reconstruction can aid in localizing bony pathology, particularly when joint resection and reconstruction are indicated (**Figure 57.4**). Less dosage but more restricted views can be obtained with cone beam CT (CBCT). The soft tissues are best imaged with MRI scanning, which will help to determine disc displacement, tears and disc movement.

Isotope bone scanning involves injecting the patient with ^{99m}Tc. This circulates the body and is taken up in bone that is actively turning over. Radiographs are taken 2 hours after injection. Uptake is increased at sites of active bone turnover and therefore will show as a 'hot spot' in a hyperplastic condyle. It will also show where there is acute infection (possibly dental). The isotope is largely expelled within 24 hours. Positron emission tomography (PET) is often used at the same time and shows similar results.

CT scans are best placed to show the bony anatomy of the joint and surrounding structures. They are essential in planning for joint replacement, but of little use in assessing the joint soft tissues. The scan itself can be used to generate a three-dimensional computer-aided design/computer-aided manufacture (CAD/CAM) model of the joint to aid planning and reconstruction.

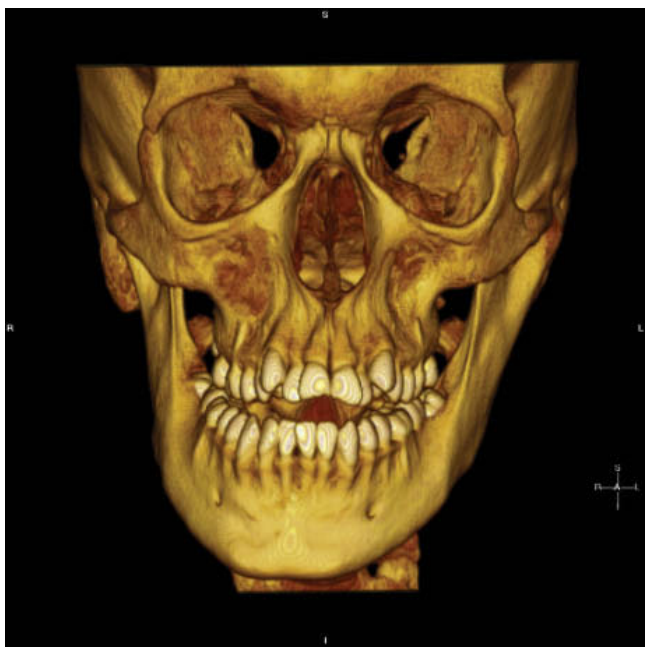


Figure 57.4 3D-CT scan showing left condylar hyperplasia with centreline deviation and lengthening of left ramus.

MRI scanning is increasingly accurate in determining the position and state of the soft tissues around the joint and the position of the disc. Unfortunately these are static scans in the most part and therefore do not look at function. Disc position can be displaced due to pain stopping the disc relocating, lack of intra-articular lubrication

or scarring within the joint holding the disc in position. This cannot be differentiated by an MRI scan and therefore the author tends not to use this modality of assessment as it seems to add little to clinical diagnosis at present. Likewise, the accuracy of the scan lies in the quality of the scan and the quality of the radiologist interpreting it. Even in the best hands, under- and over-diagnosis of disc related disease is made in 50% of cases. The wise surgeon will manage a patient according to the clinical signs and symptoms and not based solely on radiological investigations, which should be an aid to or confirmation of diagnosis.

Arthroscopy, which will be discussed in more detail later (see 'Surgical management of the TMJ' below), in good hands, provides not only a significant aid to diagnosis, but also helps to relieve over 70% of patients of their symptoms.

Open surgical exploration of the joint should only be considered as a last resort and there should be a specific pathology that the surgical treatment is aimed at relieving. It should not be considered as a diagnostic aid.

DIFFERENTIAL DIAGNOSIS

Differential diagnosis of TMJ disorders follows the standard surgical sieve. While there are numerous mnemonics for remembering this, the author finds the acronym TINNED VIIM works (**Box 57.3**).

While this surgical sieve is useful, the majority of patients presenting with TMJ symptoms have internal derangement or myofascial pain and these disorders will be dealt with first, followed by the standard surgical sieve.

INTERNAL DERANGEMENT

This condition affects up to one-third of the population at some stage during their lives. Most patients suffer nothing more than a 'clicking joint' and this is so common that some would say it is a normal variant. The clicking may be associated with pain, locking or restriction of movement. Clinical examination should determine if there is tenderness over the joints laterally and posteriorly, whether there is associated muscle tenderness and how much motion the joint can achieve by measuring the inter-incisal distance and lateral deviations. Where in the cycle the click occurs can be useful, but a determination of whether there is any glide (upper joint space movement) is more useful in determining whether there is physical restriction. Movements under 25 mm with no glide (loss of lateral deviation away from the affected side) suggest that the upper joint space is occluded, and the joint spaces are sticking together due to lack of lubrication (anchored disc phenomenon). This can be simply dealt with by early arthrocentesis if 6 weeks of conservative management fail to improve the movement.

There is often overlap of signs and symptoms of internal derangement with myofascial pain. Fortunately the initial management of both of these conditions is the same, namely rest, non-steroidal anti-inflammatory drugs (NSAIDs) and a bite splint[5] (the author uses a lower soft splint as it is cheap and easy to fit) for at least 6 weeks.

BOX 57.3 TINNED VIIM as a surgical sieve

- Congenital lesions
- Acquired lesions:
  - Traumatic
  - Inflammatory
  - Infective
  - Neoplasms:
    - primary
    - secondary
- Nutritional
- Endocrine
- Degenerative
- Vascular
- Idiopathic
- Iatrogenic
- Miscellaneous

INITIAL MANAGEMENT

The primary management of most TMJ disorders initially is reassurance that there is unlikely to be a significant underlying condition, it is unlikely to precede arthritis and the majority of patients can be managed with non-surgical treatment. A significant proportion of patients will have some psychological component to their disease process, whether this is a primary cause or a secondary effect, and the reassurance will go some way to improving their symptoms. Also the placebo effect should effect a 'cure' in around 40%. This explanation should be supported by some form of written leaflet to facilitate retention of knowledge.

Explanation of the disease process along the lines of a 'sprain' of the joint with consequent joint pain due to inflammation and resultant muscle spasm will help to empower the patient and reduce the risk of following internet mis-advice. Initial rest with avoidance of chewy foods (chewing gum and sticky toffees) and tough foods (steaks and crusty bread), and restriction of wide mouth opening (occasionally the pain may have been induced by a long dental visit) will improve symptoms, but this regime must be persisted with for several weeks. The addition of topical non-steroidal anti-inflammatory gels[6] applied to the area of the joint four times daily for 4 weeks will give additional benefit in terms of pain relief and reduction of joint inflammation. Paracetamol as a simple analgesic can additionally be used.

A lower soft full occlusal coverage splint to wear at night should be provided.[5] The patient's dentist should be able to make this. No splint has been shown to be better than any other and since a full coverage lower soft splint worn part-time is unlikely to cause untoward occlusal effects, this method is used by the author. Hard splints should cover all the teeth and make a stable occlusion. They are more costly and time consuming, but are recommended by some restorative experts. The splint helps to reduce the load on the muscles and joint overnight, particularly in those patients who have a clenching habit. It will also help to eliminate the habit. It may take a few nights for the patient to get used to the splint and it may take a few

weeks for symptoms to start to improve. There is no benefit shown by occlusal adjustment of the teeth, although some dentists may feel this is the case.[3] Cochrane analysis has shown that doing nothing is just as effective and is much less harmful.

Although physiotherapy may be beneficial in the short term there is no evidence of its long-term efficacy. Steroid injections to the joint should be avoided and it should be left to a maxillofacial surgeon to decide whether these are indicated, as repeated injections may cause joint collapse. While exercises have often been prescribed there seems to be no good evidence that they are beneficial in internal derangement. Often the exercises are poorly explained and carried out inadequately by the patient and it seems illogical to suggest that an injured joint should be exercised – imagine telling a patient with a sprained ankle they should run on it daily! Exercises may, however, be beneficial in mobilizing patients with acute muscle spasm secondary to myofascial pain or following surgery.

Following a 2-month trial of these treatments, if there has been no significant improvement, the above measures cannot be instituted or there is acute severe restriction in opening, then referral to a maxillofacial specialist, preferably with an interest in TMD, should be considered (**Box 57.4**).

Earlier intervention by means of therapeutic arthroscopy (examination and washout of the joint) or arthrocentesis is indicated in patients with restricted opening who fail to improve or in those with persistent locking. Around 80% will improve with this procedure.[7, 8] Additionally arthroscopy under general anaesthesia gives a good idea of how much of the restriction is due to muscle spasm and pain and also whether there is any intra-articular damage. Follow-up physiotherapy gives added benefit.

Where there has been no improvement following arthroscopy, and the joint was normal and mouth opening improved during anaesthesia, it is assumed that the majority of the problem is due to muscle spasm/pain and a muscle relaxant medication may be suggested. Commonly a low dose tricyclic such as amitriptylene or dothiepin is indicated with doses starting at 10 mg and potentially rising to 75 mg titrated to symptoms and side effects. These medications take around 3 weeks to become effective and doses should be increased on a monthly basis until full pain relief is achieved or side effects prevent a further increase in dose. The pain-relieving dose is maintained for 6 months and then the patient should be weaned off, according to recurrence of symptoms, over the next few weeks. Unfortunately, no long-term studies have shown benefit from this management regime. Alternative therapy currently under investigation is the injection of botulinum toxin into the areas of muscle spasm, which is effective in around 70% of patients in the author's series of more than 100 cases.[9]

Other modalities that have been used successfully in myofascial pain include cognitive behavioural therapy, in which the patient receives psychological counselling to prevent the cause of the muscle hyperactivity and manage the pain. Acupuncture may also be successful in dealing with the muscle spasm, but also the pain of internal derangement. It is however difficult to find a suitably trained specialist to manage the TMJ in particular. Transcutaneous electrical nerve stimulation (TENS) can also help in the management of the chronic pain associated with myofascial pain following failure of the other techniques.

Where arthroscopy has shown intra-articular problems these may be addressed with open joint surgery if symptoms do not improve. A variety of techniques have been used along orthopaedic principles, with, ultimately, joint replacement as the final option. The latter is not to be considered lightly and in the UK at present fewer than 100 total joint replacements are carried out each year by a small handful of recognised joint replacement surgeons. National guidelines suggest when these may be indicated.[10]

BOX 57.4 When to refer for maxillofacial advice

- Acute severe restriction of opening
- Failure of simple conservative measures in conjunction with dentist over 2 months
- Associated rheumatological disease
- Recurrent dislocation of the joint
- Disturbance of the dental occlusion

CONGENITAL

Congenital lesions of the joint are uncommon and often lead to facial asymmetry.

HEMIFACIAL MICROSOMIA

Some of the effects are due to failure of the condyle to develop, possibly secondary to loss of the blood supply in utero. This causes associated undergrowth of the ear, ear canal, joint and fossa to varying degrees. This is a complex craniofacial disorder and should be managed in a supra-regional craniofacial centre. The management involves craniofacial bone and soft tissue reconstruction in various stages throughout life. It may occur on both sides.

CONDYLAR HYPERPLASIA

This is due to either overgrowth of the condylar growth centre on one side before or during puberty, or continued growth after completion of puberty with cessation of growth on the contralateral side. The patient will present with progressive disturbance of the occlusion, usually with centreline deviation of the dental centreline and associated deviation of the chin point (hemimandibular hyperplasia) (see **Figure 57.2**). It may also present with bowing of the mandible downwards and associated maxillary dentoalveolar compensatory growth with the occlusion developing a downward cant towards the side of the abnormality (hemimandibular hypertrophy). There is not

usually associated pain, although in the adult onset version there may be limited translatory movement of the TMJ on the affected side.

Diagnosis is aided by seeing an elongated condylar neck on OPG (pubescent type) or an abnormal condyle (post-pubescent). Ongoing growth can be confirmed by an isotope bone scan using ^{99m}Tc or a PET scan. These will both show increased uptake on the affected active side. Management where there is increased uptake is to remove the growth plate by means of a condylar shave procedure where the cartilage growth centre is removed surgically.[11] If the disease is burnt out or has been treated by condylar shave, the resultant deformity and centreline correction is managed by orthognathic surgery (jaw realignment). These procedures require referral to a maxillofacial surgeon.

TRAUMATIC

Trauma to the TMJ is a common occurrence in fractures of the mandible. The majority of facial fractures in the UK are related to interpersonal violence. Condylar fractures are one of the more common mandibular fractures, occurring in around 30% of cases. They may also occur bilaterally or be associated with fractures elsewhere on the bony mandible. Occasionally the fracture may involve the temporal bone (with haemotympanum) or may cause perforation of the external auditory canal (with associated bleeding form the external canal).

In children fractures of the condyle tend to occur within the capsule and are difficult to treat operatively. Diagnosis in a child follows a direct blow over the joint or an indirect blow to the mandible elsewhere, particularly the chin. The child will complain of pain in the area, difficulty opening the mouth fully and sometimes inability to close the teeth together due either to bone displacement (contralateral open bite) or fluid within the joint (ipsilateral open bite) secondary to intra-articular soft tissue injury. There will be swelling and tenderness over the area of the fracture and the occlusion may be disrupted as above.

Initial management is often with mobilization and analgesia as this injury can affect the secondary growth plate in the condyle, causing undergrowth, overgrowth or fusion of the joint surfaces (ankylosis). Intermaxillary fixation (holding the teeth together with elastics or wires) for a 2–4-week period may be considered where the occlusion is deranged. Occasionally, internal fixation may be considered with resorbable plates.

Effusion or haemarthrosis should be managed with arthrocentesis to enable joint recovery.

The child should be monitored long term to observe for growth abnormalities such that these can be treated at a stage when compensatory growth has not occurred to such an extent to make future management more difficult.

In the adult the fracture pattern is often different. Extra-capsular fractures are more common. Symptoms and signs are similar to those in children with pain over the site of the injury and on function, swelling and possible malocclusion. If the occlusion is normal then the fracture is managed non-operatively with a soft diet and mobilization for 4–6 weeks. Derangement of the occlusion warrants management either with intermaxillary fixation of some variety or, in some cases, open reduction and internal fixation with miniplates may be required. There is considerable controversy as to the best way of managing these fractures and the reader is referred to the standard maxillofacial trauma texts if they are interested in considering this further. Growth disturbances and ankylosis are much less common in adults. Dislocation into the middle cranial fossa has been rarely described. These injuries should all be managed by a suitably trained oral and maxillofacial surgeon.

INFECTIVE TMJ DISORDERS

Infection of the TMJ is an uncommon occurrence in the developed world. It does, however, remain a major source of morbidity.

Infection may be due to direct infection of the joint, from local spread from the surrounding structures or due to deposition from a distant site, usually from a polyarticular infective processes.

Primary infection may be of the intra-capsular bone – osteomyelitis – or infection of the intra-articular soft tissues – arthritis. Both can be destructive of bone and soft tissues and lead to either joint collapse or ankylosis (fusion) of the joint. In childhood they will lead to secondary growth arrest with subsequent deformity. The usual organism is *Staphylococcus aureus* in immune competent individuals, with other staphylococci or unusual organisms where the host is immunocompromised.

The most common cause of infection is spread from neighbouring structures of the ear, brain and nasopharynx. All of the organisms causing mastoiditis, otitis media and meningitis can be implicated, but again *Staphylococcus* spp. are most likely to invade the joint. The effects of the infection long-term are similar to those from direct infection, but in children ankylosis often ensues.

Haematogenous spread rarely occurs, but is occasionally secondary to enteric organisms (*Salmonella* spp.) or systemic organisms causing a more generalized polyarthritis (syphilis, bacterial endocarditis, septicaemia). Effects are similar to the other two causes, but often the systemic infective process carries more morbidity and risk of mortality.

Diagnosis is from a history of pain and swelling localized to the area of the joint, with acute onset limitation of movement. The patient will have generalized signs of an infective process with pyrexia, rigors, sweating (particularly night sweats) and malaise. They may also have signs and symptoms of other joint involvement. Locally there will be the signs of acute inflammation with tenderness over the joint, swelling, redness and heat. There may be additional cervical lymphadenopathy and tenderness over the mastoid if there is middle ear involvement.

The diagnosis can be confirmed with aspiration of pus from the joint and this should be sent for urgent culture and sensitivities. The patient should be admitted

to hospital and broad spectrum intravenous antibiotics should be commenced with thorough arthrocentesis of at least 500 ml of isotonic solution or until the aspirate is clear. This should be repeated if necessary. The advice of a microbiologist should be sought for local sensitivities in guidance for antibiotic treatment. General systemic support would include antipyretic (paracetamol and NSAID) and adequate hydration, with management of the causative disease process. Systemic involvement with septicaemia may require admission to intensive care.

Ultimate management may involve open surgical drainage. The long-term sequelae of the process may require further surgical input and early maxillofacial surgical advice is essential, in addition to long-term support. Reconstruction and rehabilitation may require open surgical procedures, osteotomies, rib grafts or joint replacement.

INFLAMMATORY DISEASE OF THE TMJ

Many of the inflammatory arthropathies can affect the TMJ.[12] Rheumatoid disease can occur in the child, adolescent and adult. It will usually present with the signs and symptoms of synovitis, namely pain, swelling, heat and restriction of movement, and therefore can be difficult to differentiate from infective causes. Progression can lead to joint collapse resulting in malocclusion with an anterior open bite and a retrusive chin (see **Figure 57.3**). Usually other joints, particularly the hands and feet, will have been involved for some time, as rheumatoid disease is a polyarticular arthropathy tending to affect the smaller joints. Diagnosis can be confirmed serologically with a positive rheumatoid factor present in 80%. Sero-negative arthropathy can occur with a similar clinical picture. In the head and neck there can be associated dry mouth, dry eyes (Sjögren's syndrome) and difficulty with oral hygiene due to involvement of the hands.

Management of the rheumatoid TMJ should initially follow the same principles as for most TMJ disorders. Rest, with a soft diet and avoidance of wide opening, NSAIDS (topical or systemic) regularly and a soft splint to rest the muscles, which may be overactive, and to offload the joint. Early consideration of arthroscopy and arthrocentesis will help to eliminate the inflammatory mediators from within the joint. If synovitis is active then steroid injection should be considered, although repeated injections, which calm down the inflammatory process, may lead to increased cartilage loss and joint collapse. End-stage management of the collapsed joint is with total joint replacement. A rheumatologist should be involved as they may instigate disease-modifying medication.

Ankylosing spondylitis may initially present similarly in the TMJ. The patients are mostly male and tend to have generalized signs with fixed kyphosis (flexion of the spine, particularly the neck). Classically they are HLA-B27 positive, although this is not exclusive to ankylosing spondylitis. The process leads to ankylosis of the TMJ, and the restriction of mouth opening is made worse by the fixed flexion of the neck towards the chest wall (see **Figure 57.1**). Release of the ankylosis surgically with joint reconstruction is required, optimally with total joint replacement to give a large enough gap to prevent reankylosis and enable adequate function. Fat graft interposition is suggested to reduce the risk of reankylosis.

Psoriatic arthropathy may affect the TMJ, causing acute synovitis, joint collapse or ankylosis. The patients initially present with the skin condition of psoriasis (although up to 50% have minimal skin signs and these may need to be carefully sought out), with involvement often of the larger joints in a degenerative type of arthropathy. Some patients may be HLA-B27 positive and these tend to progress towards an ankylosis picture rather than the synovitis that often characterizes this disease process. Management of the synovitis is with rest, NSAIDs and bite splints. Arthrocentesis can help relieve symptoms, as can steroid injections. Ultimately joint replacement may be required due to joint collapse or ankylosis.

All of the rheumatoid diseases may be managed by a rheumatologist with disease-modifying medication, which may have significant side effects on the oral mucosa and may also interact with various other medications. Routine dental care is essential as the patient may have difficulty with oral care due to hand disability, or have a dry mouth. Bisphosphonates may be used, particularly with osteopenic rheumatoid conditions, and due diligence in general dental management with support to prevent disease to the oral structures is essential such that the occurance of bisphosphonate related osteonecrosis can be prevented. Leucocyte inhibition medication may cause mild immunosuppression and aggressive management of infection is essential in these patients. Stopping these medications prior to any form of surgery should be discussed with the rheumatologist as they can inhibit wound healing.

NEOPLASTIC DISEASE OF THE TMJ

Neoplasms may be primary or secondary, benign or malignant. Primary benign neoplasms of the TMJ are rare and include chondroma, synovial chondromatosis, osteochondroma and osteoma. Malignant neoplasms are even more uncommon and the condyle seems to be preserved when the mandible is invaded by squamous carcinoma. Chondrosarcoma, osteochondrosarcoma and osteosarcoma are extremely rare in the head and neck and even more so in the condyle. They are dealt with elsewhere in this book. The slightly anomalous pigmented villonodular synovitis behaves as a neoplasm with locally invasive tendency, but again is rare.

Benign neoplasms tend to slow growth (the commonest being osteochondroma) and therefore can present with pain, loss of movement and slowly progressive deformity with a lateral open bite on the side of the neoplasm. There is occasional centreline shift of the chin and dental centreline, but more commonly downward bowing of the lower border of the mandible occurs. Diagnosis is from clinical and radiological examination, supported, if necessary, by open joint surgery to biopsy or excise the lesion

and subsequent reconstruction and/or orthognathic correction of the resultant malocclusion and facial deformity.

Synovial chondromatosis is a rare condition that affects the joint, often secondary to degenerative disease. Production of large numbers of small chondromata from the synovium occurs, producing numerous millimetre-sized, rounded loose bodies in the joint. These affect joint function (with pain, locking and noises) and can induce pain. Management is with open washout as they are often too large to pass through an arthroscope. This should allow the joint to function although there is often degenerative change that warrants surgical treatment in its own right. It is felt to be due to overproduction of cartilage by the synovium and therefore synovectomy is advocated.

Metastasis may occur to the condyle as to any other region of the mandible. The common neoplasms metastasizing to bone include breast, kidney, thyroid, and colon with osteolytic lesions and the prostate with osteosclerotic lesions. Diagnosis and management of the primary site is essential, but the metastasis should be managed symptomatically with either resection and reconstruction, radiotherapy or pain management.

DEGENERATIVE DISEASE OF THE TMJ (OSTEOARTHROSIS)

This is the final common pathway for a number of TMJ conditions from trauma, infection, inflammation, neoplastic and iatrogenic causes. Primary degenerative disease can also occur but it is much less common than involvement of the knee and hip. Overuse causing bone compression is the often-quoted reason for any degenerative joint disorder. Internal derangement of the joint is a very common condition that does not usually lead to degenerative osteoarthrosis if the wear and tear component of this disease can be converted to repair by appropriate non-invasive interventions. It is much less common than degenerative disease of the major joints as the load is significantly less in the TMJ. It tends to occur when the wear and tear in the joint overtakes the repair. Pain, swelling and restriction of movement are the common symptoms. Clinical examination reveals a tender joint with palpable crepitus and restriction of movement, with intermittent swelling.

Radiographic findings are more noticeable on CT scan and include sclerosis, loss of joint space, osteophytes and erosions or cyst formation.

Initial management is with conservative measures followed by arthroscopy, open surgery and, ultimately, joint replacement as above.

IATROGENIC/IDIOPATHIC

The former use of open joint surgery for pain, restriction and joint noises has led to the increasing frequency of degeneration of the joint from multiple operations, particularly in the USA. Surgery for joint noise alone has now been accepted as inappropriate. Less commonly, however, patients following open surgery may have dysaesthetic pain due to damage to the surrounding nerves. This is a debilitating type of pain, which is difficult to manage. It may be of a shooting nature or dull background ache with acute exacerbations. Management under the direction of a pain team is indicated and is usually with low dose tricyclic antidepresants or antiepileptic medication (carbamazepine, gabapentin, etc.).

SURGICAL MANAGEMENT OF THE TMJ

Surgery of the joint can be divided into closed and open surgery. Closed surgery comprises arthrocentesis and arthroscopy.

Arthrocentesis is the washing out of (usually) the upper joint space with isotonic solution under pressure (recommended 150 mm Hg) using around 200 ml of solution to eliminate inflammatory mediators and free radicals and to re-lubricate the joint initially with the solution, but allowing the lubricant producing cells to recover. Usually two needles are used to carry out this procedure – inlet and outlet. Whilst this procedure can be performed under local anaesthesia potentially with sedation, the preference in the UK is for general anaesthesia (GA). The advantage of carrying out the procedure under GA is that the patient can be examined with the muscles relaxed, giving a good idea of the degree of restriction due to muscle spasm. It is a day case procedure and has been shown to be successful in improving 70–80% of cases of locking, restriction and pain.[1, 7, 8]

Arthroscopy is a similar procedure, although a small rigid fibre-optic endoscope is inserted into the joint rather than two needles. A needle is still used as the outlet. The scope size varies from internal diameter of 2.1 mm, although disposable endoscopes of 1.2 mm are now available. There is some debate regarding the advantage of arthroscopy over arthrocentesis, as the insertion of a larger scope should carry more morbidity. The rationale behind inserting a scope is to aid in diagnosis, not outcome. The outcomes are similar for arthroscopy and arthrocentesis, but arthrocentesis does not see into the joint and will miss diagnoses of disc damage, joint surface damage, scarring and synovitis, and the accuracy of this technique in experienced hands is very high.[13] There have been no comparisons of complications with arthrocentesis and arthroscopy and no long-term obvious detrimental effects of arthroscopy have been reported, other than an ~1% risk of temporary temporal branch weakness of the facial nerve.

Open joint surgery follows the principles of orthopaedics. The joint is approached via a pre-auricular incision, staying close to the cartilaginous auditory meatus to avoid damage to the temporal branch of the facial nerve. If there is damage to the disc this is removed and may or may not be replaced with temporalis muscle flap or auricular cartilage, although there has not been any benefit shown to providing this replacement. Damage to the joint surfaces can be improved using eminoplasty (modification of the articular eminence) or condylar shave (modification of the condylar head). The outcomes of this surgery following

failed arthroscopy are around 60% discharge with manageable symptoms.[14]

Severe degeneration of the joint with associated pain and restriction of opening, ankylosis or inflammatory joint disease with joint collapse warrant joint replacement. Whilst this was often with a costochondral graft (rib), recently alloplastic joint replacement has become the mainstay of treatment using a combination of cobalt-chrome and titanium or all titanium on high molecular weight polyethylene for replacement (similar to total knee replacement). Outcomes of 90% joint survival at 15 years[15] are reported with improvement of dietary scores and pain of 90% at one year[16] and significant improvements in mouth opening. The frequency of use of this procedure warrants, at present, the surgery only being carried out in limited numbers by a few high volume operators, although the indications seem to be increasing. For this reason NICE guidelines have suggested indications for this line of management.[17]

CONCLUSION

Temporomandibular disorders are a common cause of morbidity in general practice, although most can be managed with simple measures, such as reassurance that joint noises do not require any form of management and do not necessarily lead to degenerative joint disease. The final common pathway of a number of conditions is degenerative disease and surgery should be considered a last resort.

KEY POINTS

- TMJ problems are largely managed conservatively with little requirement for surgical input.
- Most TMJ problems do not progress to arthritis.
- Symptoms include pain, restriction of opening, locking and joint noises.
- Signs include tenderness/spasm in muscles of mastication, limitation in opening < 35 mm, deviated mouth opening, joint line tenderness, rarely malocclusion.
- Initial management is rest, topical anti-inflammatories, muscle massage and a bite splint.
- Early arthrocentesis is useful in acute severe restriction of opening.
- Arthroscopy is both diagnostic and therapeutic.
- Open surgery should only be considered where arthroscopy has demonstrated an abnormality which has not responded.
- Joint replacement is the final common pathway and should only be undertaken by a surgeon with experience and training in this technique.

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CHAPTER
58

ANATOMY OF THE LARYNX AND TRACHEOBRONCHIAL TREE

Nimesh N. Patel and Shane Lester

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SEARCH STRATEGY

Data in this chapter are based on a PubMed search using the keywords: larynx, airway, trachea, bronchi and pulmonary.

INTRODUCTION

The human larynx protects the lower respiratory tract, provides a controlled airway, allows phonation and allows the generation of a high intrathoracic pressure for coughing and lifting. The evolution of the larynx provides an insight into its functional priorities. In its most primitive form, it can be found as a muscular sphincter around the entrance to the respiratory tract in the Bichir lungfish (*Polypterus bichir*), controlling the entry of water and the expulsion of air from the lungs. A further evolutionary variant is seen in the Mexican salamander, which possesses lateral cartilages that aid in opening and maintaining patency of the respiratory tract. The ability of the larynx to facilitate speech is only found in humans and represents a more specialized function of the larynx; it is, therefore, a very late evolutionary event.

To fulfil its complex functions the larynx has to be mobile, coordinated and sensate. In rehabilitating the damaged larynx there is often a need to make a trade-off between optimum airway, voice and swallowing.

EMBRYOLOGY

Embryology of the larynx

At four weeks of embryonic development, an outgrowth of the primitive foregut forms the primordial respiratory system. The epithelium of the larynx, trachea and bronchi is of endodermal origin and the other soft tissues arise from the surrounding splanchnic mesoderm (fourth and sixth branchial arches).

The traditional theory of respiratory system embryology states that there is initially a wide communication with the foregut, which expands and becomes separated by two longitudinal oesophagotracheal ridges. These were thought to fuse to form a septum dividing the ventral trachea and lung buds from the dorsal oesophagus. More recent research supports assertions that the respiratory diverticulum develops from the ventral aspect of the foregut and elongates, drawing out a stalk and giving rise to the trachea (**Figure 58.1**). It is proposed that the septum is present from the initial appearance of the lung buds and that there is no migration of the separation point while the trachea descends.

When moving in a craniocaudal direction, the larynx, which is formed at the most cranial end of the respiratory tract, then leads to the trachea, bronchi and lungs. These tubes of endoderm, which project ventrally from the foregut, elongate into the surrounding mesenchyme from which the connective tissue, cartilage, non-striated muscle and vasculature of the bronchi and lungs develop.

Arytenoid swellings appear on both sides of the tracheobronchial diverticulum and, as they enlarge, the epithelial walls of the groove adhere to each other, and the aperture of the larynx is occluded until the third month, when the lumen is restored. The rudimentary laterally based arytenoid swellings elongate cranially, creating a cleft that is open cranially and bounded laterally by the aryepiglottic folds. More ventrally, at the front of this cleft, the hypobranchial eminence becomes the epiglottis.

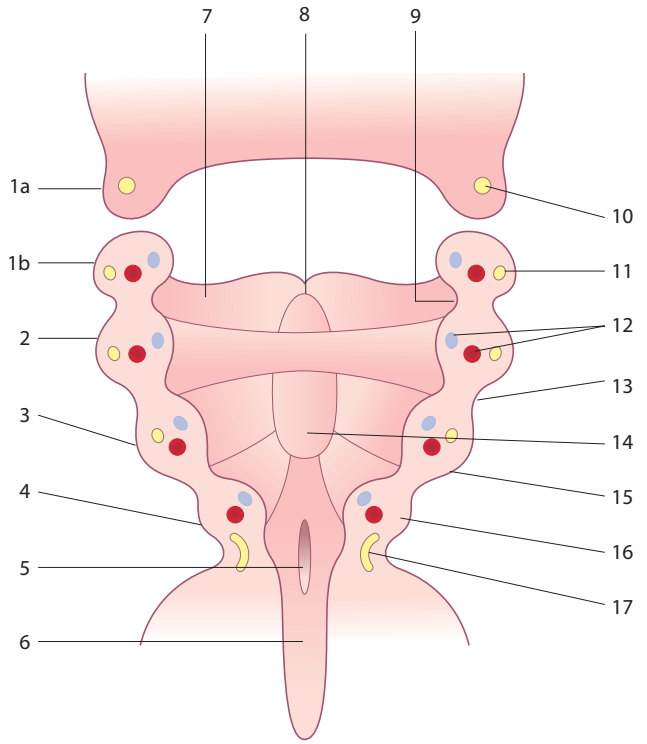

Figure 58.1 1) Arches and elevations in the floor of the foregut; 1a) First arch, maxillary process; 1b) first arch, mandibular process; 2) second pharyngeal arch; 3) third pharyngeal arch; 4) fourth pharyngeal arch; 5) tracheobronchial diverticulum; 6) oesophagus; 7) endodermal lining; 8) tuberculum impar; 9) first pharyngeal pouch; 10) maxillary nerve; 11) mandibular nerve; 12) cartilage and artery; 13) second pharyngeal cleft; 14) hypobranchial eminence; 15) ectodermal covering; 16) mesenchyme in fourth arch; 17) superior laryngeal nerve.

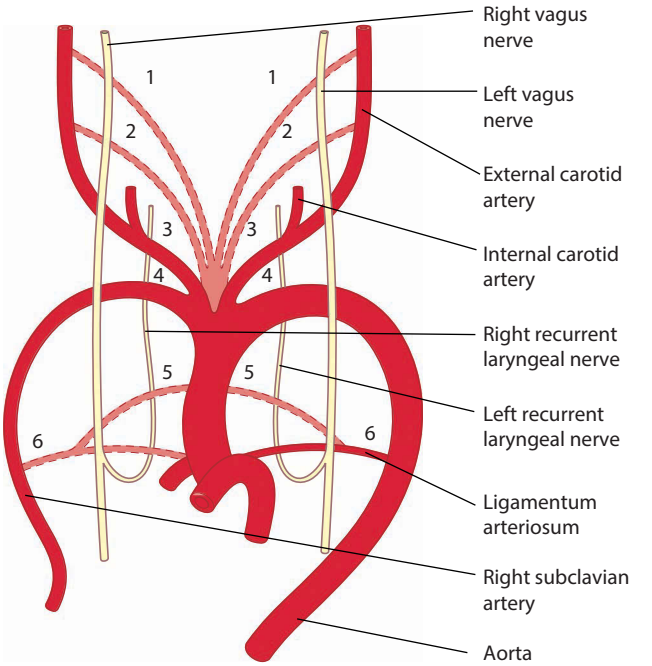

Figure 58.2 The relationship between development of the branchial arches and recurrent laryngeal nerves. The numbers indicate the number of the branchial arch.

The glottis forms just above the level of the primitive aperture. Surrounding this, the thyroid cartilage develops from the ventral ends of the cartilages formed in the mesoderm of the fourth pharyngeal arch and appears as two lateral plates, each of which possesses two chondrification centres. The cricoid cartilage and the cartilages of the trachea develop from the sixth arch during the sixth week of gestation. The trachea rapidly increases in length in a craniocaudal direction from the fifth week of gestation onwards.

The mesoderm of each pharyngeal arch differentiates into the cartilage, muscle and vascular structures of that arch. As part of its dorsoventral direction of development, each arch receives an afferent and efferent nerve supply for the skin, muscles and endodermal lining of that arch, which in the case of the fourth and sixth arches are the superior and recurrent laryngeal branches of the vagus nerve respectively. The primitive recurrent laryngeal nerve enters the sixth visceral arch on each side below the sixth aortic arch artery. On the left side, the arch artery retains its position as the ductus arteriosus so the nerve is found below the ligamentum arteriosum after birth. On the right side, the dorsal part of the sixth arch artery and the whole of the fifth arch artery disappear, leaving the nerve below the fourth arch artery, which becomes the subclavian artery (**Figure 58.2**). Occasionally, the proximal portion of the fourth arch artery also disappears leaving nothing in contact with the right recurrent laryngeal nerve, which, instead of being pulled down into its usual position, passes directly from the main vagal trunk to enter the larynx, demonstrated as the non-recurrent laryngeal nerve.

Embryology of the trachea and bronchial tree

The trachea and the two lateral bronchial buds form from the lung bud and at the fifth week each bronchial bud develops into a main bronchus. The right goes on to form three secondary bronchi, the left developing into two. They continue to grow caudally and laterally, expanding into the developing body cavity. During further development there are further divisions of the buds in a dichotomous fashion. By the end of the sixth month there are approximately 17 generations of subdivisions. An additional 6 divisions occur during postnatal life to form the final structure of the pulmonary tree.

ANATOMY OF THE LARYNX

General description

The larynx extends from the laryngeal inlet to the inferior border of the cricoid cartilage (**Figure 58.3**). In the absence of respiration at neutral lung volume, it lies in front of the third to sixth cervical vertebrae, being a little higher in women than in men.

The infantile larynx is proportionally smaller than that of the adult compared to body size and is more

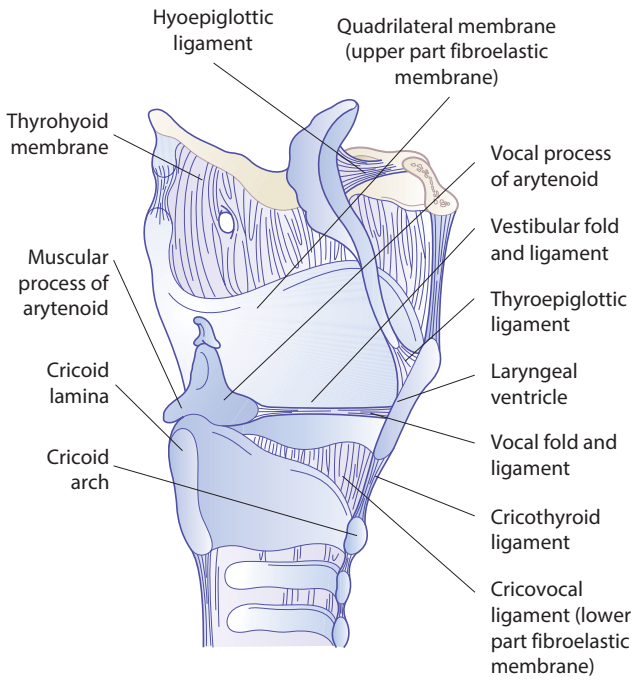

Figure 58.3 Sagittal section across the larynx looking laterally.

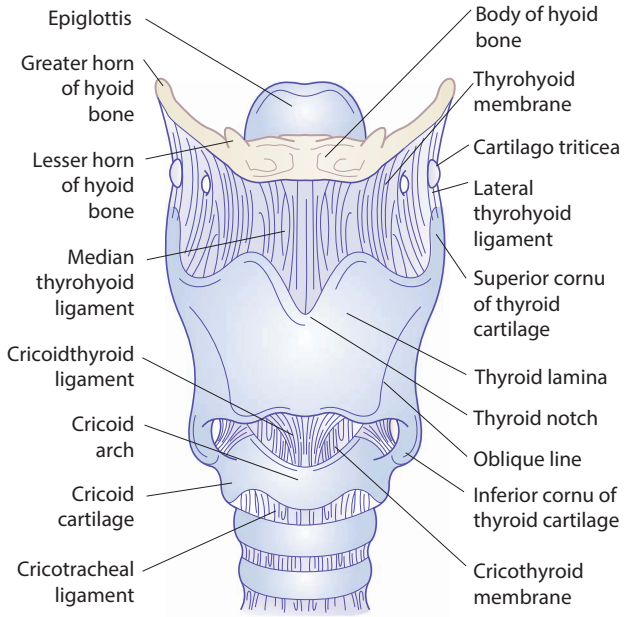

Figure 58.4 The framework of the larynx.

funnel shaped. Its narrowest part is at the junction of the subglottic larynx with the trachea and even a slight swelling in this area may result in marked airway obstruction. In contrast, the narrowest part of the adult larynx is the glottis. The laryngeal cartilages are much softer in the infant than the adult and collapse more easily on forced inspiration as a consequence of the Bernoulli effect. The larynx starts high up under the tongue in early life and with age assumes an increasingly lower position in the neck. As the larynx grows, there is little difference in its size between boys and girls until after puberty when the anterior–posterior (AP) diameter of the larynx almost doubles in men to reach a final AP dimension average of about 36 mm in men and 26 mm in women.

The larynx is divided anatomically into the supraglottis, glottis and subglottis by the false and true folds (see **Figure 58.3**). The term 'vocal cord' is not anatomically accurate; the term vocal fold is more appropriate. Vocal cord is an inaccurate term that has remained in common use and fails to emphasize the layered structure of the vocal fold. In addition, the term 'cord' does not give a sense of a structure that might vibrate in the vertical (and indeed multiplanar) fashion that the vocal folds have been shown to do.

In a craniocaudal direction, the supraglottis commences at the epiglottis and aryepiglottic folds as they sweep down to the arytenoids. Its lower border is a horizontal line drawn through the apex of the laryngeal ventricle. This line, therefore, also forms the upper border of the glottis. The glottis extends caudally from this line and includes the vocal cords as well as anterior commissure and posterior commissure. The line of demarcation between the glottis and the subglottis has been debated in the literature at some length but is now widely accepted to be a line drawn 1 cm below the free edge of the vocal folds. More definitively, the subglottis becomes the trachea at the lower border of the cricoid.

The framework of the larynx consists of the hyoid bone and a number of cartilages connected by ligaments and membranes, as well as intrinsic and extrinsic muscles. It is lined with a mucous membrane that is continuous above with the pharynx and below with that of the trachea. The spaces around the larynx are filled with adipose tissue and loose connective tissue, the 3D orientation of which are key to understanding the spread of tumours within the larynx.

The framework of the larynx

HYOID BONE

The hyoid is a U-shaped bone that is suspended by several suprahyoid muscles and ligaments from the bony structures of the skull base and mandible, and provides the superior attachment for many of the extrinsic muscles of the larynx, thereby suspending the larynx in the neck (**Figure 58.4**). The hyoid bone consists of a body anteriorly from which the greater cornua project backwards on each side. The lesser cornua are two small conical eminences that are attached to the upper aspect of the body of the hyoid laterally (and sometimes from the medialmost aspect of the greater cornua), either by a fibrous band or, sometimes, by way of a synovial joint.

THYROID CARTILAGE

The thyroid cartilage is composed of two laminae that are fused in the midline anteriorly giving rise to the laryngeal prominence (see **Figure 58.4**). The angle of fusion is about 90° in men and 120° in women. The posterior border of

each lamina is prolonged above and below to form the superior and inferior cornua, respectively. The superior cornu is long and narrow and curves upwards, backwards and medially, ending in a conical extremity to which the lateral thyroid ligament is attached. The inferior cornu is shorter and thicker and curves downwards and medially. On the medial surface of its lower end is a small oval facet joint for articulation with the cricoid cartilage.

On the external surface of each lamina, an oblique line curves downwards and forwards from the superior thyroid tubercle, situated just in front of the root of the superior horn, to the inferior thyroid tubercle on the lower border of the lamina. This line marks the attachment of the thyrohyoid, sternothyroid and inferior constrictor muscles. On the inner aspect of the thyroid cartilage, just below the thyroid notch in the midline, is attached the thyroepiglottic ligament and below this and on each side of the midline, are attached the vestibular and vocal ligaments and thyroarytenoid, thyroepiglottic and vocalis muscles. The fusion of the anterior ends of the two vocal ligaments produces the anterior commissure tendon. The remaining parts of the inner aspect of the thyroid lamina are smooth and are mainly covered by loosely attached mucous membrane. The superior border of each lamina gives attachment to the thyrohyoid ligament and the inferior border, on the medial portion of its inner aspect, the cricothyroid ligament.

CRICOID CARTILAGE

The cricoid cartilage is the only complete cartilaginous ring in the airway (**Figure 58.5**). It forms the inferior part of the anterior and lateral walls and most of the posterior wall of the larynx. It has a deep broad lamina posteriorly and a narrow arch anteriorly with a facet for articulation with the inferior cornu of the thyroid cartilage, near the junction of the arch and lamina. Rotation of the cricoid cartilage on the thyroid cartilage can take place about an axis passing transversely through both joints. The lamina has sloping shoulders on which the articular facets for the arytenoid cartilages are found. A vertical ridge in the midline of the lamina gives attachment to the longitudinal muscle of the oesophagus and produces a shallow concavity on each side for the origin of the posterior cricoarytenoid (PCA) muscle. The entire inner surface of the cricoid cartilage is lined with mucous membrane. The importance of the cricoid in laryngeal health and disease cannot be overemphasized. The luminal mucosa is at risk of necrosis and circumferential scarring, which results in debilitating subglottic stenosis. The cricoarytenoid joint – together with an associated functional PCA muscle – is regarded as a key functional unit of the larynx, facilitating vocal fold motility to ensure a patent airway when abducted and airway protection when adducted.

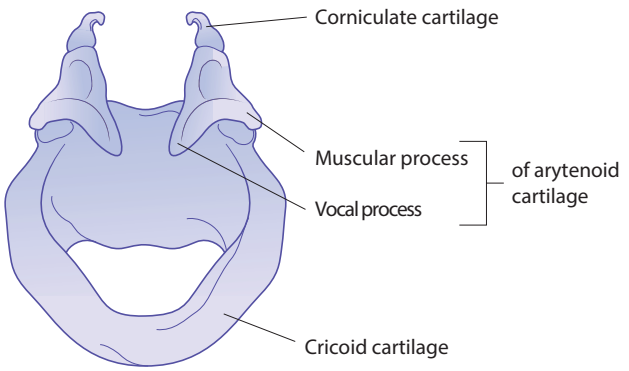

Figure 58.5 The cricoid and arytenoids.

THE ARYTENOID CARTILAGES

The arytenoid cartilages are irregularly shaped, broadly conforming to a three-sided pyramid with a forward projection, the vocal process, to which the dorsal end of the vocal folds are attached a lateral projection, the muscular process, to which the posterior cricoarytenoid and lateral cricothyroid muscles attach (see **Figure 58.5**). Between these two processes, the anterolateral surface is irregular and divided into two fossae by a crest running from the apex. The upper triangular fossa gives attachment to the vestibular ligament and the lower to the vocalis and lateral cricoarytenoid muscles. The apex is curved backwards and medially and is flattened for articulation with the corniculate cartilage, which sits atop it. The medial surfaces have no muscular attachments, are covered with mucous membrane and form the lateral boundary of the posterior glottis. The posterior surface of each cartilage is covered by the transverse arytenoid muscle, which inserts onto each cartilage across the midline.

The base is concave and presents a smooth surface for articulation with the sloping shoulders of the upper border of the cricoid lamina. This is a synovial joint with lax capsular ligaments allowing both rotatory movements and medial and lateral gliding movements. However, the posterior cricoarytenoid ligament is more rigid and prevents forward movement of the arytenoid cartilage on the cricoid.

CORNICULATE AND CUNEIFORM CARTILAGES

The corniculate cartilages (of Santorini) are two small conical nodules of elastic fibrocartilage, which articulate through a synovial joint with the apices of the arytenoid cartilages. They are situated in the posterior part of the aryepiglottic fold. The cuneiform cartilages (of Wisberg) are two small, elongated flakes of fibroelastic cartilage, one in each free margin of the aryepiglottic fold. The function of these cartilages is uncertain. They may act to provide structural rigidity to the aryepiglottic folds somewhat like curtain weights.

EPIGLOTTIS

The epiglottis is a thin, leaf-like sheet of elastic fibrocartilage that projects upwards behind the tongue and the body of the hyoid bone. It is attached inferiorly to the thyroid cartilage, just below the thyroid notch in the midline, by the thyroepiglottic ligament and also to the hyoid bone anteriorly by the hyoepiglottic ligament. The space between

these ligaments forms the pre-epiglottic space. From the sides of the epiglottis, the aryepiglottic folds sweep downwards and backwards to the apex of the arytenoids. The posterior (laryngeal) surface of the cartilage is indented by numerous small pits into which mucus glands project. The anterior (lingual) surface of the epiglottis is covered with mucous membrane superiorly and forms the posterior wall of the vallecula. The mucous membrane overlying the epiglottis is reflected onto the base of the tongue, forming the glossoepiglottic fold in the midline and laterally the lateral glossoepiglottic folds.

Ligaments and membranes of the larynx

EXTRINSIC LIGAMENTS

The extrinsic ligaments of the larynx connect the laryngeal cartilages to the hyoid above and trachea below (see **Figure 58.4**). Superiorly, the thyrohyoid membrane stretches between the upper border of the thyroid cartilage and the posterior surface of the body and greater cornua of the hyoid. The membrane is composed of fibroelastic tissue, reinforced by fibrous tissue in the midline as the median thyrohyoid ligament and posteriorly as the lateral thyrohyoid ligament. The latter connects the tip of the superior cornua of the thyroid cartilage to the posterior ends of the greater cornua of the hyoid. The ligaments often contain a small nodule of cartilage, the cartilago triticea. The membrane is pierced by the internal branch of the superior laryngeal nerve and by the superior laryngeal vessels. The cricotracheal ligament unites the lower border of the cricoid with the first tracheal ring.

INTRINSIC LIGAMENTS

The intrinsic ligaments of the larynx connect the laryngeal cartilages together, strengthen the capsule of the intercartilaginous joints and form a broad sheet of fibroelastic tissue, the fibroelastic membrane, which lies beneath the mucous membrane of the larynx forming an internal framework (see **Figures 58.3** and **58.6**).

The fibroelastic membrane is divided into an upper and lower part by the laryngeal ventricle. The upper quadrilateral membrane extends between the lateral border of the epiglottis and the arytenoid cartilages. The upper margin forms the framework of the aryepiglottic fold and the lower margin is thickened to form the vestibular ligament underlying the vestibular fold (false vocal fold). The lower part is thicker, containing many elastic fibres. It is commonly called the cricovocal ligament, cricothyroid ligament or conus elasticus. It is attached below to the upper border of the cricoid cartilage and above it is stretched between the inner surface of the midpoint of the laryngeal prominence of the thyroid cartilage anteriorly and the vocal process of the arytenoid behind. The free upper border of this membrane constitutes the vocal ligament the framework of the (true) vocal fold. Anteriorly, there is a thickening of the membrane, the cricothyroid ligament, which connects the cricoid and the thyroid cartilages in the midline.

Muscles of the larynx

The extrinsic muscles of the larynx attach the larynx to neighbouring structures and maintain the position of the larynx in the neck (**Table 58.1**). The infrahyoid muscles work in synergy with the elevators of the larynx, one set of muscles relaxing (infrahyoid) whilst the other contracts (suprahyoid) to facilitate laryngeal elevation. Under normal physiological conditions, descent of the larynx is due to elastic recoil of the trachea and lower respiratory tract and therefore, relaxation of the suprahyoid musculature is the only requirement.

The intrinsic muscles are all paired and function in a coordinated fashion to move the cartilages of the larynx thereby governing laryngeal function (**Table 58.2** and **Figures 58.7–58.11**). They control the overall position and shape of the vocal folds as well as the elasticity and viscosity of each layer. The majority of intrinsic muscles act to move the arytenoid at the cricoarytenoid joint. The joint has a complex range of movements but broadly speaking the arytenoid rotates inwards and downwards to close and upwards and outwards to open the glottis.

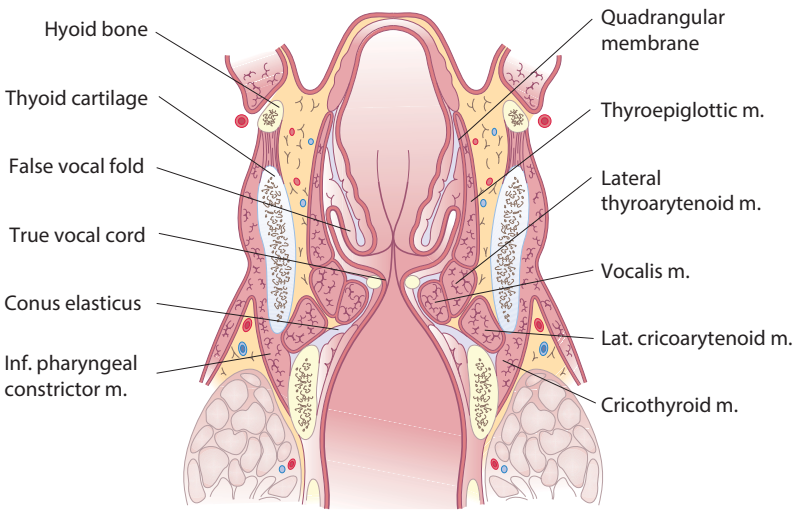

Figure 58.6 Coronal section through the larynx looking anteriorly.

TABLE 58.1 Extrinsic muscles of the larynx

Name	Origin	Insertion	Function	Innervation
Infrahyoid group				
Thyrohyoid	Oblique line of thyroid lamina	Inferior border of the greater cornu of the hyoid	Elevates the larynx on a fixed hyoid or depresses the hyoid on a fixed larynx	Hypoglossal (C1 root)
Sternothyroid	Posterior surface of manubrium and edge of the first costal cartilage	Oblique line of the thyroid lamina	Depresses the larynx	Ansa cervicalis (C2, 3 roots)
Sternohyoid	Clavicle and posterior surface of the manubrium	Lower edge of the body of the hyoid	Depresses the larynx by lowering the hyoid	Ansa cervicalis (C1, 2, 3 roots)
Suprahyoid group				
Mylohyoid	Mylohyoid line on inner aspect of the mandible	Midline raphe and body of the hyoid	Raises and pulls the hyoid anteriorly	Nerve to mylohyoid (inferior alveolar branch of V3)
Geniohyoid	Genial tubercle on mandible	Upper border of the body of the hyoid	Raises and pulls the hyoid forwards	Hypoglossal (C1 root)
Stylohyoid	Back of the styloid process (splits around the digastric tendon)	Base of greater cornu of the hyoid	Retractor and elevator of the hyoid for swallowing	Facial nerve
Digastric	Digastric notch on the medial surface of the mastoid process	Lower border of the mandible (fibrous sling holds the tendon to the lesser cornu of the hyoid)	Anterior belly pulls the hyoid anteriorly and up	Posterior belly – facial nerve
			Posterior belly pulls the hyoid posteriorly and up	Anterior belly – nerve to mylohyoid
Stylopharyngeus	Medial aspect of the styloid process	Posterior border of the lamina of the thyroid cartilage (side wall of the pharynx)	Elevates the larynx	Glossopharyngeal nerve
Palatopharyngeus	Palatine aponeurosis and posterior margin of hard palate	Posterior border of thyroid alar and cornua	Helps tilts the larynx forwards	Accessory nerve (pharyngeal plexus)
Salpingopharyngeus	Eustachian tube	Posterior border of the thyroid cartilage (side wall of the pharynx)	Elevates the larynx	Pharyngeal plexus

The posterior cricoarytenoid is the only abductor of the larynx – and is arguably, therefore, the most important muscle in the body. The thyroarytenoids cause some adduction but largely shorten and thicken whilst altering the tension of the vocal fold. The interarytenoid muscles draw the arytenoids together posteriorly whilst the lateral cricoarytenoid muscles internally rotate the arytenoid cartilages by pulling their muscular processes caudally and anteriorly resulting in vocal fold adduction.

The cricothyroid muscles are the only intrinsic muscle that do not insert into the arytenoid cartilages; they therefore exert their action by bringing the thyroid and cricoid cartilages closer together in a visor-like motion. In doing so both vocal folds are simultaneously stretched with a consequence increase in tension.

Some muscles are able to exert more than one action and therefore possess segmental compartmentalization. For example, the posterior cricoarytenoid has two components with different fibre types, nerve branches and insertions into the muscular process of the arytenoid, which allows for external and backward rotation of the arytenoid cartilage on the cricoarytenoid joint. (See **Table 58.1** for additional examples.)

The glottis

The glottis lies between two horizontal lines, one drawn through the apex of the laryngeal ventricle, the other drawn 1 cm below the medial free edge of the vocal fold when the larynx is at rest. The scaffolding of the false and true vocal folds is formed by the vestibular and vocal ligaments, respectively (see **Figures 58.3** and **58.6**). Laterally, intervening between the vestibular and vocal ligaments, a horizontal slit opens into an elongated recess, the laryngeal ventricle. From the anterior part of the ventricle, the saccule of the larynx ascends between the vestibular ligament and the inner surface of the thyroid cartilage as high in some people as the upper border of the thyroid cartilage. It occasionally protrudes through the thyrohyoid membrane. Fibrous tissue surrounds the saccule. Dilatation of the saccule results in the formation of a laryngocele. The ventricle and saccule can harbour occult cancers and need to be actively inspected during diagnostic endoscopy.

The vestibular folds are thick folds of mucous membrane scaffolded on a narrow band of fibrous tissue, the vestibular ligament, which is the lower border of the upper quadrilateral membrane. It is fixed in front at the angle of the

TABLE 58.2 Intrinsic muscles

Name	Origin	Insertion	Function	Effect
Open and close the glottis				
Posterior cricoarytenoid	Lower and medial surface of the back of the cricoid lamina	It fans out to be inserted into the back of the muscular process of the arytenoid	Opens the glottis. Upper horizontal fibres rotate the arytenoids and move the muscular processes towards each other separating the vocal processes and abducting the cords. Lateral vertical fibres draw the arytenoids down the sloping shoulders of the cricoid separating the arytenoids	Abducts and elevates the tip of the vocal process The vocal fold becomes elongated and thin. The free edge of the vocal fold is rounded and passively stiffened
Lateral cricoarytenoid	Superior border of lateral part of the arch of the cricoid	Muscular process of arytenoid	Adducts and lowers the tip of the vocal process by rotating the arytenoids medially	Vocal fold adducted, lowered, elongated and thinned. The edge of the vocal fold becomes sharp and is passively stiffened
Transverse arytenoids – unpaired	Posterior surface of the muscular process and outer edge of the arytenoid	Crosses over and attaches to the same point on the other arytenoid	Adducts the vocal fold and controls the position of the vocal fold	No significant effect on the mechanical properties of the vocal fold
Oblique arytenoids – paired	Posterior aspect of the muscular process (superficial to the transverse arytenoid)	Apex of the other arytenoid		
Control the tension of the vocal folds				
Thyroarytenoid (vocalis): A broad sheet of muscle which lies lateral to and above the free edge of the cricovocal ligament. The lower part of the muscle is thicker and forms a distinct bundle called the vocalis muscle.	Back of the thyroid prominence and cricothyroid ligament	Vocal process of arytenoid and anterolateral surface of the body of the arytenoid		Lowers, shortens and thickens the vocal folds causing the edge of the fold to be rounded. The body of the fold is actively stiffened but the transition layers are passively slackened. Many fibres are prolonged into the aryepiglottic fold some continuing to the margin of the epiglottis as the thyroepiglottic muscle which tends to widen the inlet of the larynx pulling the aryepiglottic folds slightly apart
Cricothyroid: This is the only intrinsic muscle that lies outside the cartilaginous framework of the larynx	Lateral surface of the anterior arch of the cricoid. Fibres fan out and pass backwards in two groups	Lower oblique fibres pass backwards and laterally to the anterior border of the inferior cornu of the thyroid cartilage. Anterior straight fibres ascend to the posterior part of the lower border of the thyroid lamina		Rotates the cricoid cartilage about the horizontal axis passing through the cricothyroid joint. It lengthens the vocal folds by increasing the distance between the angle of the thyroid cartilage and arytenoids. On contraction, the vocal folds are brought into a line between the anterior commissure and the posterior cricoarytenoid ligament, the level of the vocal folds is lowered and the entire fold elongated and thinned. The edge of the vocal fold becomes sharp and all the layers are stiffened
Alter the shape of laryngeal inlet				
Aryepiglotticus: A continuation of the oblique arytenoid	Posterior aspect of the muscular process of the arytenoid	Fibres pass around the apex of the opposite arytenoid and insert into the aryepiglottic fold		Weak sphincter of the laryngeal inlet
Thyroepiglotticus: A continuation of the thyroarytenoid	Back of the thyroid prominence and cricothyroid ligament	Fibres pass upwards into the aryepiglottic fold		Widens the inlet of the larynx pulling the aryepiglottic folds slightly apart

All the intrinsic muscles of the larynx are supplied by the recurrent laryngeal nerve except the cricothyroid, which is supplied by the external branch of the superior laryngeal nerve. The unpaired transverse arytenoid and paired oblique arytenoid make up the interarytenoid muscle.

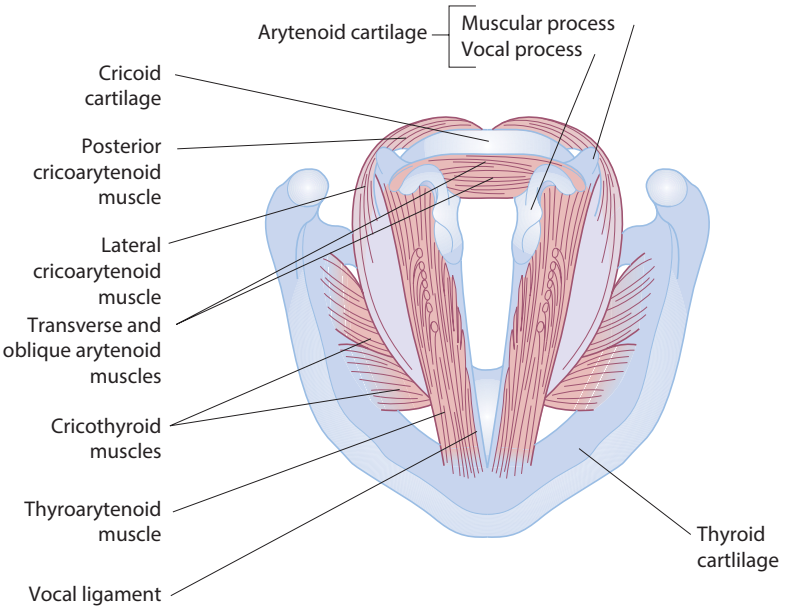

Figure 58.7 Dissected view of the larynx from above

thyroid cartilage just below the attachment of the epiglottic cartilages and behind the anterolateral surface of the arytenoid cartilage just above the vocal process (see **Figure 58.7**).

The vocal folds extend from the middle of the angle of the thyroid cartilage to the vocal process of the arytenoid cartilages and scaffolding them is the upper border of the conus elasticus. Each fold is a layered structure consisting of a superficial layer of nonkeratinizing, stratified squamous epithelium, beneath which is the lamina propria. This has three distinct layers. The superficial layer (Reinke's space) contains a fibrous substance with similar characteristics to gelatin. The intermediate layer contains elastic fibres and the deep layer collagen fibres. The intermediate and deep layers make up the vocal ligament. The vocalis muscle, which forms the main body of the vocal fold, lies lateral and deep. The loose areolar tissue of Reinke's spaces allows lax movement of the overlying mucosa, giving rise to a mucosal waveform during phonation.

The layered structure of the vocal fold is not uniform in its entire length. At the anterior end of the vocal fold there is a mass of collagen fibres (anterior commissure tendon or Broyle's ligament), which are connected to the inner perichondrium of the thyroid cartilage and to the deep layer of the lamina propria posteriorly. Adjacent to this mass of collagen fibres just posteriorly, there is another mass of elastic fibres continuous with the intermediate layer of the lamina propria called the anterior macula flava. A similar structure is seen at the posterior end of the membranous part of the vocal fold. These structures appear to serve as cushions to protect the ends of the vocal folds from mechanical damage caused by vocal fold vibration.

The anterior three-fifths of the vocal fold (from the anterior commissure to the tip of the vocal process) is the membranous part. The remaining two-fifths posteriorly extend from the tip of vocal process to the face of the arytenoid cartilage, and are called the cartilaginous part of the vocal fold. The height of the vocal folds diminishes towards the anterior commissure mainly because the inferior edge of the vocal fold slopes upwards. At the anterior commissure the lower edges of the vocal folds form the apex of a triangle via Broyle's ligament to the epiglottis, so tumour involving the anterior commissure readily involves the subglottis. The vocal folds are therefore almost wedge shaped, with the 'blunted' apex of the wedge anteriorly.

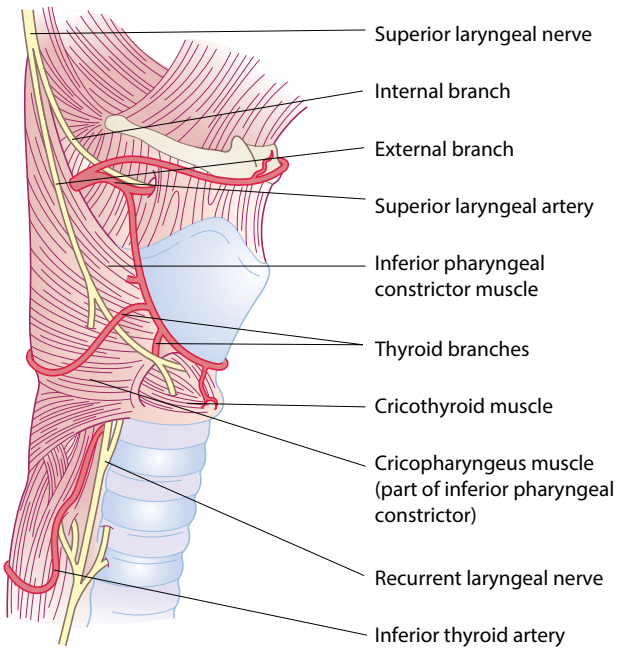

Figure 58.8 Lateral view of the larynx (complete).

Mucous membranes of the larynx

The mucous membrane lining of the larynx is closely attached over the posterior surface of the epiglottis, the corniculate and cuneiform cartilages and over the vocal ligament. Elsewhere, it is loosely attached and prone to oedema. Most of the larynx is lined by pseudostratified ciliated columnar 'respiratory'-type epithelium. The upper half of the posterior surface of the epiglottis, the upper

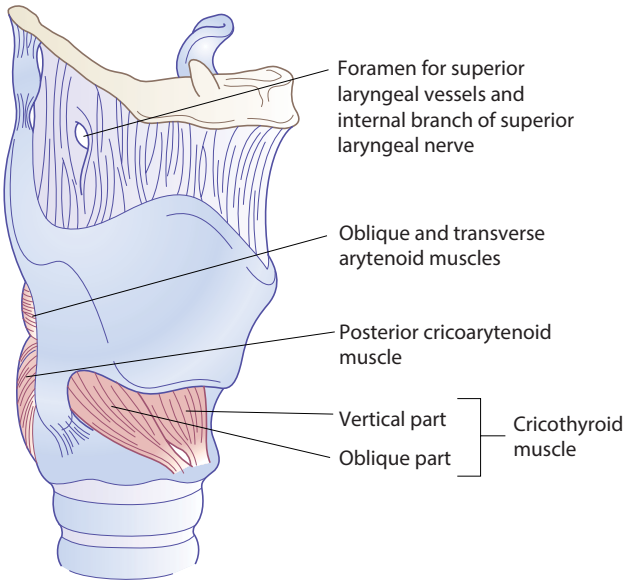

Figure 58.9 Lateral view of the larynx with extrinsic muscle removed.

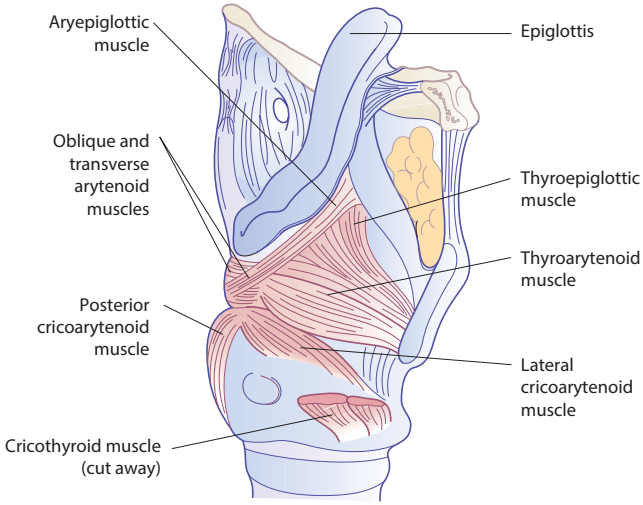

Figure 58.10 Lateral view of the larynx with the ipsilateral thyroid cartilage and cricothyroid muscle removed.

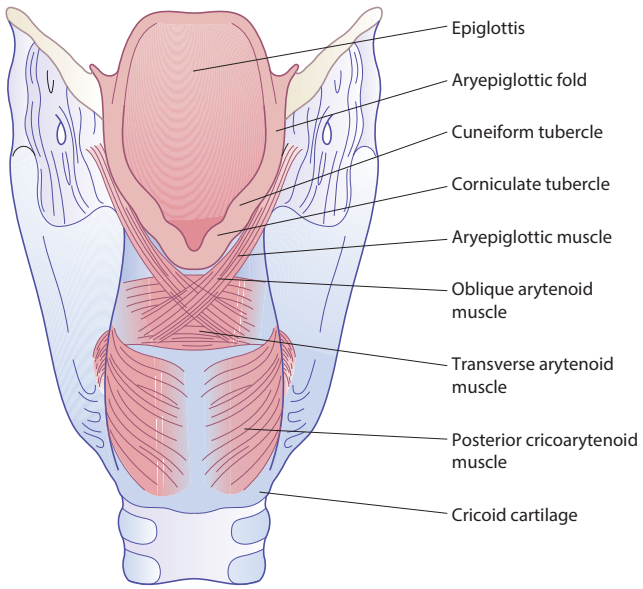

Figure 58.11 Posterior view of the larynx.

part of the aryepiglottic fold, the posterior glottis and the vocal folds are covered with non-keratinizing stratified squamous epithelium.

Mucous glands are freely distributed throughout the mucous membranes and are particularly numerous on the posterior surface of the epiglottis where they form indentations into the cartilage and in the margins of the lower part of the aryepiglottic folds and in the saccules. The vocal folds do not possess any glands and the mucous membrane is lubricated by mucus from the glands within the saccules. The squamous epithelium of the vocal folds is therefore prone to desiccation if these glands cease to function, for example after radiation.

Spaces within the larynx

Spaces in the larynx contain fat, lymphatics and vessels. They represent potential pathways of tumour spread that may have a significant bearing on treatment and prognosis.

PRE-EPIGLOTTIC SPACE

The pre-epiglottic space is a wedge-shaped space with the point of the wedge inferiorly (see **Figure 58.3**). It is bounded anteriorly by the thyrohyoid ligament and hyoid bone and posteriorly by the epiglottis. Superiorly, the hyoepiglottic ligament connects the epiglottis to the hyoid bone. Tumour may spread into this area through small perforations in the epiglottis or directly through the hyoepiglottic ligament. The pre-epiglottic space is continuous laterally with the paraglottic space as no anatomical boundaries exist.

PARAGLOTTIC SPACE

The paraglottic space is bounded laterally by the thyroid cartilage, medially by the conus elasticus and quadrangular membrane and posteriorly by the piriform fossa mucosa. It contains the laryngeal ventricles and saccules (see **Figures 58.7** and **58.12**). Tumours may spread extensively in this submucosal space in the absence of significant mucosal changes

Nerve supply of the larynx

The motor and sensory nerves of the larynx are derived from the vagus by way of its superior and recurrent laryngeal nerves (see **Figure 58.8**). The superior laryngeal nerve arises from the inferior ganglion of the vagus and receives a branch from the superior cervical sympathetic ganglion. It descends lateral to the pharynx behind the internal carotid artery and at the level of the greater horn of the hyoid divides into a small external branch and a larger internal branch. The external branch provides motor supply to the cricothyroid muscle, while the internal branch pierces the thyrohyoid membrane above the entrance of the superior laryngeal artery and divides into two main sensory and secretomotor branches. The upper branch

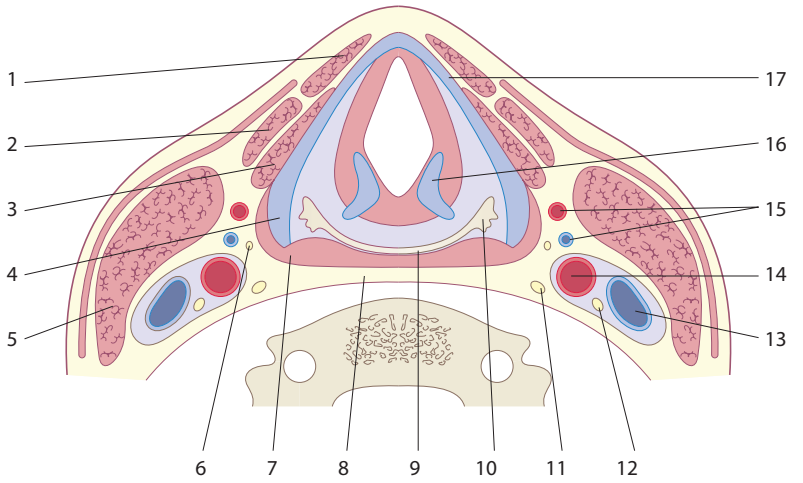

Figure 58.12 Axial section at C5 showing the relationship of the larynx to the surrounding structures. 1) Sternohyoid; 2) omohyoid; 3) thyrohyoid; 4) thyroid cartilage; 5) sternocleidomastoid; 6) external laryngeal nerve; 7) inferior constrictor muscle; 8) retropharyngeal space; 9) hypopharynx; 10) pyriform fossa; 11) cervical sympathetic ganglion; 12) vagus nerve; 13) internal jugular vein; 14) internal carotid artery; 15) superior thyroid artery and vein; 16) arytenoid cartilage; 17) vocal fold.

supplies the mucous membrane of the lower part of the pharynx, epiglottis, vallecula vestibule of the larynx and the lower branch descends in the medial wall of the piriform fossa beneath the mucous membrane and supplies the aryepiglottic fold and the mucous membrane of the larynx down to the level of the vocal folds. In its course beneath the mucous membrane of the medial wall of the piriform fossa, the superior laryngeal nerve is accessible for injection of local anaesthesia, providing excellent anaesthesia for most of the piriform fossa. The internal branch of the superior laryngeal nerve also carries afferent fibres from neuromuscular spindles and other stretch receptors in the larynx. The superior laryngeal nerve ends by piercing the inferior constrictor of the pharynx and unites with an ascending branch of the recurrent laryngeal nerve. This branch is called Galen's anastomosis and is purely sensory.

The right recurrent laryngeal nerve leaves the vagus as it crosses superficial to the right subclavian artery and loops under the artery, ascending in the tracheoesophageal groove to reach the larynx. On the left, the nerve originates from the vagus as it crosses the aortic arch. It then passes under the arch and the ligamentum arteriosum to reach the tracheoesophageal groove. In the neck, both nerves follow the same course and pass upwards accompanied by the laryngeal branch of the inferior thyroid artery. They pass deep to the lower border of the inferior constrictor muscle and enter the larynx behind the cricothyroid joint. The recurrent laryngeal nerve then divides into motor and sensory branches. The motor branch has fibres derived from the cranial root of the accessory nerve, which supply all the intrinsic muscles of the larynx except the cricothyroid. The sensory branch supplies the laryngeal mucosa below the level of the vocal folds and also carries afferent fibres from stretch receptors in the larynx.

There is some evidence to suggest there are variable anastomoses between the internal and recurrent laryngeal nerves. The existence of a 'laryngeal plexus' or multiple anastomoses may explain the variable clinical presentations of laryngeal nerve injuries and recovery from laryngeal injury.

The relationship between the recurrent laryngeal nerve and the inferior thyroid artery is variable. The nerve may cross in front of or behind the artery, or may pass between the terminal branches of the artery. On the right there is an equal chance of the nerve being in any of three locations in relation to the artery, although on the left it is more likely to lie posterior to the artery.

Laryngeal vasculature

ARTERIAL

The arterial supply of the larynx is derived from laryngeal branches of the superior and inferior thyroid arteries and the cricothyroid branch of the superior thyroid artery (see **Figure 58.8**). The superior laryngeal artery arises from the superior thyroid artery and passes deep to the thyrohyoid muscle. Together with the internal branch of the superior laryngeal nerve, it pierces the thyrohyoid membrane to supply the larynx. The superior laryngeal artery can be injured in endoscopic laryngeal laser surgery as it enters the paraglottic space at the anterior end of the aryepiglottic fold. Therefore, meticulous care to ensure haemostasis must be taken during supraglottic endoscopic surgical resections. The inferior laryngeal artery arises from the inferior thyroid artery at the level of the lower border of the thyroid gland and ascends on the trachea with the recurrent laryngeal nerve. It enters the larynx beneath the lower border of the inferior constrictor to supply the larynx. The cricothyroid artery is a branch of the superior thyroid artery and passes across the upper part of the cricothyroid ligament to supply the larynx. This ligament is penetrated by the branches (up to five) of the cricothyroid artery, which can be injured during cricothyroidotomy or endoscopic resection of anterior commissure cancers.

The arteries of the larynx form a communicating plexus in the paraglottic space, which can be the source of brisk bleeding during endolaryngeal surgery.

VENOUS

The veins leaving the larynx accompany the arteries. The superior laryngeal veins enter the internal jugular vein by way of the superior thyroid or facial vein. The inferior laryngeal veins drain into the inferior thyroid veins, which connect with the brachiocephalic vein. Some veins drain into the middle thyroid vein and then into the internal jugular vein.

LYMPHATIC DRAINAGE

The lymphatic drainage of the larynx is separated, by the vocal folds, into upper and lower drainage systems. The larynx above the vocal folds is drained by vessels that accompany the superior laryngeal vein and pierce the thyrohyoid membrane emptying into the upper deep cervical lymph nodes. The larynx below the vocal folds drains to the lower deep cervical chain, often through prelaryngeal (Delphian) and pretracheal nodes. The vocal folds themselves are firmly bound down to the underlying vocal ligament and there are no lymphatics present in this plane. Early cancers of the vocal folds do not therefore readily spread to the lymph nodes.

ANATOMY OF THE TRACHEA AND BRONCHIAL TREE

General description

THE TRACHEA

The trachea is a pathway for ventilation and clearance of bronchial secretions. It begins at the lower border of the cricoid cartilage and ends at the carina (**Figure 58.13**). The average length of the adult male trachea is 11.8 cm (range 10–13 cm). It has an ovoid shape, with average external diameters 2.3 cm (anteroposterior) by 1.8 cm (transverse) in the male and 2.0 cm by 1.4 cm in the female. The diameter of the paediatric trachea is 3 mm at birth.

The trachea slopes backwards from an anterior position in the neck to a posterior position in the mediastinum, at an angle that varies with age and spinal position. The trachea is mobile, moving upwards in swallowing and down and forwards on inspiration. The relatively fixed position of the left main bronchus under the arch of the aorta means that with any degree of kyphosis, the position moves more towards the horizontal and can limit the amount of trachea that is brought into the neck by extension of the neck.

The cross section of the trachea is D-shaped with incomplete C-shaped cartilaginous rings. The free posterior ends of cartilage embed into the smooth muscle trachealis, which has longitudinal and transverse fibres. There are approximately 2 rings per centimetre of trachea with each ring averaging 4 mm in length. This corresponds to 18–22 rings in the tracheal wall, which is approximately 3 mm thick. The size of the tracheal lumen may be altered by age and by disease.

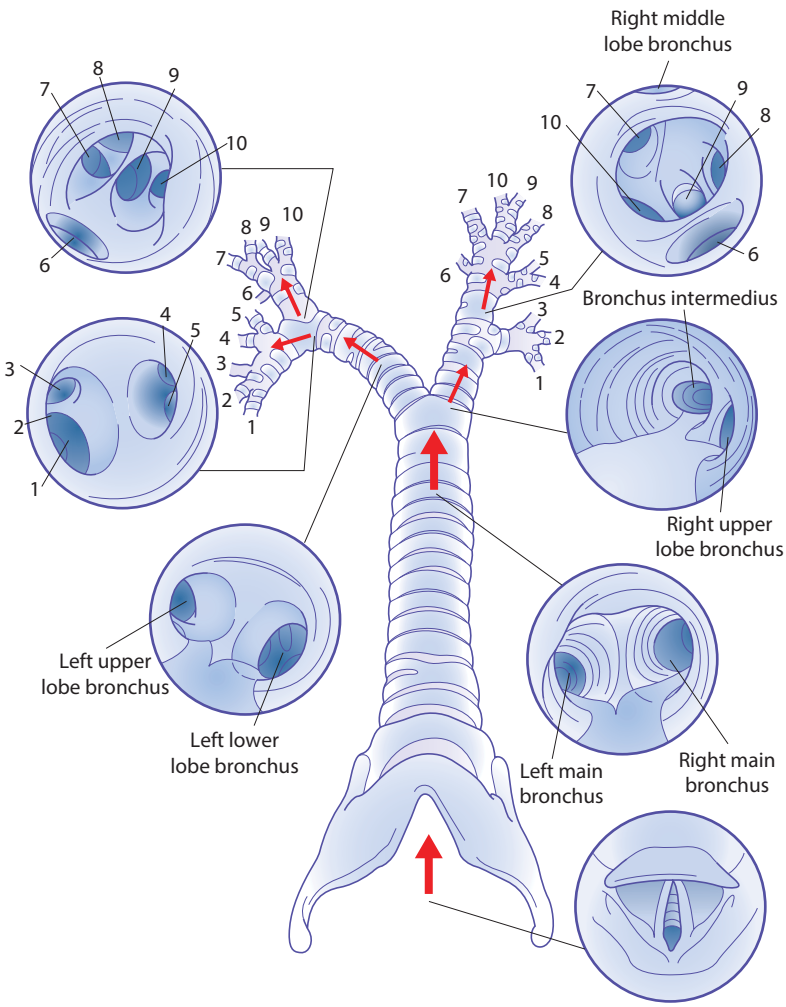

Figure 58.13 The tracheobronchial tree and views seen on endoscopy. Right lung, upper lobe bronchus: 1, apical; 2, posterior; 3, anterior, middle lobe bronchus; 4, lateral; 5, medial, lower lobe bronchus; 6, apical; 7, medial basal (cardiac); 8, anterior basal; 9, lateral basal; 10, posterior basal. Left lung, upper lobe bronchus.

THE CARTILAGES

The C-shaped cartilage rings line the trachea and bronchi where they both stiffen the wall and provide a degree of flexibility. Two or more cartilages may unite, either partially or completely, or bifurcate. Their elasticity may decrease with age as they become increasingly calcified.

The first cartilage is broader and may be joined to the cricoid cartilage or it may be separated with clearly defined cricotracheal ligament. The last ring above the carina is thick and broad and forms a bridge between the right and left main bronchi with a downwards curving triangular process continuing from the inferior border, which forms the posterior of the carina.

THE FIBROUS MEMBRANE AND TRACHEALIS

Each cartilage is enclosed in and nourished by perichondrium, which is continuous with an enveloping fibrous membrane. The membrane consists of a dense sheet of irregular connective tissue encircling the rings of cartilage, trachealis and the deficient posterior borders of the extrapulmonary bronchi. Composed of collagen and elastin fibres in crossing orientations, they permit expansion and aid elastic recoil of the airways. Constriction of the tracheal lumen is facilitated by trachealis, the transverse fibres inserting into the perichondrium at the free margins of the cartilage rings. The longitudinal trachealis fibres and the outer fibrous layer blend in with the fascia over the oesophagus and loose areolar fibres of the mediastinum.

THE MUCUS MEMBRANE

The lining of the upper airways is pseudo-stratified, ciliated, columnar epithelium with numerous goblet cells, resting on a broad basement membrane. The cilia beat the mucus blanket upwards towards the larynx and eventually the pharynx, where it is swallowed. The lamina propria is rich in longitudinal elastin fibres and overlies a submucosa of loose connective tissue containing the neurovascular structures, tubular glands and lymphoid patches.

The epithelium becomes thinner with increasing branching of the segmental bronchi. There are fewer goblet cells and a thinner basement membrane. Eventually the epithelium becomes a single layer. The smaller airways have less cartilage and are relatively more muscle until the circular muscle fibres are almost circumferential within the cartilage, rather than the fibromuscular tissue found higher up in airway. Contraction of these muscles, which form an interlacing network of fibres, both shortens and constricts the segmental bronchi.

CARINA AND BRONCHI

The trachea bifurcates and narrows slightly at the carina with the origin of the left and right main bronchi (**Figure 58.13**) at the level of T5 (posteriorly) and the manubrium (anteriorly). The right main bronchus makes an angle of 25–30 degrees with the carina, less than the 45-degree angle made by the left main bronchus. Therefore aspirated foreign bodies are more likely to continue into the right rather than left main bronchus.

RIGHT MAIN BRONCHUS AND BRANCHES

With an adult length of approximately 5 cm and a diameter of 17 mm (+/– 4 mm) in men and 15mm (+/– 4 mm) in women, the right main bronchus lies above the right pulmonary artery and below the azygos vein. The bronchus continues as the bronchus intermedius after take-off of the right upper lobe bronchus at a distance of 12–20 mm from the carina, and further down this terminates in the middle and lower lobe bronchi (see **Figure 58.13**).

The right upper lobe bronchus is approximately 1 cm long and divides into an apical, posterior and anterior segmental bronchi, which supply the right upper lobe. A variation of this anatomy exists where the apical segmental bronchus originates from the trachea at the level of the carina.

The right middle lobe bronchus arises approximately 2.5 cm down the bronchus intermedius, and terminates in lateral and medial segmental bronchi. The segmental bronchi of the right lower lobe consist of superior, anterior basal, posterior basal, medial basal and lateral basal divisions.

LEFT MAIN BRONCHUS AND BRANCHES

At 5.5 cm in length, the left main bronchus is longer, but 2–3 mm narrower than the right. It crosses anterior to the oesophagus, thoracic duct and descending aorta, travelling inferior to the aortic arch. The left pulmonary artery lies first anterior then superior to the left main bronchus, which terminates in the left hilum at the level of T6 as the upper and lower lobe bronchi.

The left upper lobe bronchus divides into apico-posterior (which further subdivides into apical and posterior) and anterior segmental bronchi (see **Figure 58.13**). The upper lobe bronchus terminates in the lingular bronchus, which gives superior and inferior segmental bronchi.

Similar to the right side, the left lower lobe bronchus gives five segmental bronchi-apical (superior), lateral basal and posterior basal and the final two medial basal (cardiac), anterior basal, which share a common stem.

Neurovascular supply of the tracheobronchial tree

NERVE SUPPLY

The recurrent laryngeal nerves provide motor supply to the smooth musculature and also carry sensation from the mucosa. Sympathetic supply derives mainly from the middle cervical ganglion and interconnects with the recurrent laryngeal nerves. The lungs are supplied by the anterior and posterior pulmonary plexuses situated at the hilum of each lung.

Parasympathetic supply of the trachea and bronchi is from the vagus with efferent stimulation provoking

bronchoconstriction, glandular secretion and vasodilatation. Vagal afferents are involved in the cough reflex.

BLOOD SUPPLY

The blood supply enters the lateral walls of the trachea in a distributed segmental fashion. The cervical trachea receives its blood supply from the inferior thyroid artery. Most often the upper half of the trachea is supplied by three tracheoesophageal branches of the inferior thyroid artery. The branches may pass anterior or posterior to the recurrent laryngeal nerves. The 2nd and 3rd branches also supply the oesophagus.

The segmental arteries to the trachea branch superiorly and inferiorly over the width of several tracheal rings, forming a series of longitudinal anastomoses along the lateral walls of the trachea. The arterial branches also give anterior and posterior branches near to the tracheal wall. The anterior branches further anastomose near the midline. The posterior branches supply the membranous wall, which also receives supply from the oesophageal arteries. The veins drain to the inferior thyroid plexus.

The bronchial tree and carina receives its arterial supply via the bronchial arteries, of which there are usually three. Two of these are on the left and are direct branches from the aorta. On the right the bronchial artery comes from the third right posterior intercostal artery. The bronchial veins drain into a superficial system, draining into the azygos vein on the right and the accessory hemiazygos on the left. The deep drainage, which also drains the lung parenchyma, drains into the pulmonary veins.

LYMPHATIC DRAINAGE

The lymphatics in the trachea and bronchi arise in a submucosal plexus and connect with a plexus in the outer fibrous membrane, where pulmonary associated lymph nodes are located. The pulmonary nodes drain into the bronchopulmonary nodes found at the points of subdivision of the airway. The subcarinal nodes are important as they drain from both lungs and drain into the ipsilateral para-tracheal nodes. Lymphatics from the trachea drain into the pretracheal and eventually into the para-tracheal groups of nodes (level VI), which also drain the superior tracheobronchial nodes.

The para-tracheal nodes drain into the vessels from the internal thoracic and brachiocephalic lymph nodes to form the bronchomediastinal trunks, which drain into the right lymphatic duct and the left sided thoracic duct.

Surgical anatomy

TRACHEA

The trachea is covered from deep to superficial by skin, superficial and deep cervical fascia, sternohyoid and sternothyroid muscles and, for a variable distance, the thyroid isthmus (**Figure 58.14**). The isthmus usually lies over the second to fourth tracheal cartilages but can vary in size and thickness with age and disease.

In the lower neck the trachea is anteriolaterally related to the inferior thyroid artery (when present) and anteriorly to the inferior thyroid veins and the thymus gland, which can be large and fleshy in infants. In the mediastinum the left brachiocephalic vein and artery, the arch of the aorta, the left common carotid artery, the deep part of the cardiac plexus and pre-tracheal lymph nodes are located anterior to the trachea (**Figure 58.15**). In infants the brachiocephalic artery crosses the trachea at a higher level, just as it descends behind the suprasternal notch. The brachiocephalic vein, due to a relatively higher position in the neck in infants, is at risk with surgical access to the trachea, as it may lie above the suprasternal notch.

Lateral relations of the trachea are the lobes of thyroid gland, carotid sheath and contents and para-tracheal nodes. Postero-laterally the recurrent laryngeal nerves run in the tracheo-oseophageal groove and the oesophagus is located posteriorly.

HILUM OF THE LUNG

The hilum of the lung is enclosed in a sheath of pleura and is the entry and exit for pulmonary structures.

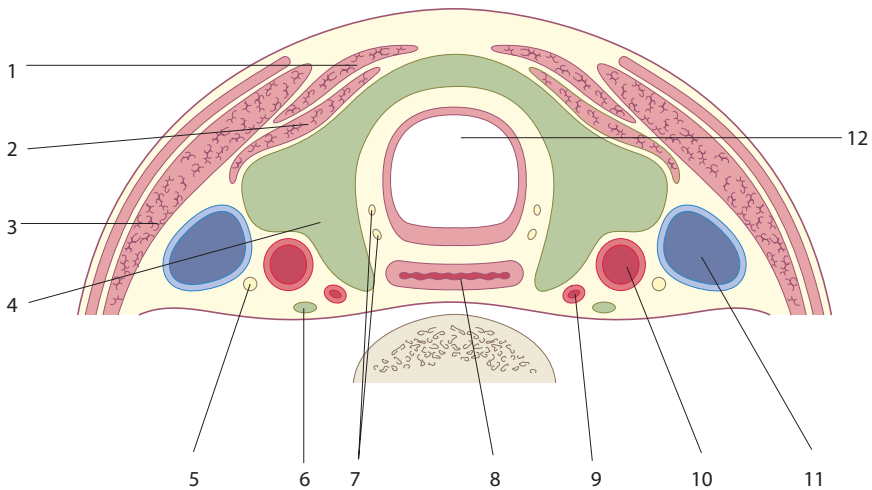

Figure 58.14 Axial section at C7 showing the relationship of the upper trachea to surrounding structures. 1, Sternohyoid muscle; 2, sternothyroid muscle; 3, sternocleidomastoid muscle; 4, thyroid gland; 5, left vagus nerve; 6, cervical sympathetic ganglion; 7, left recurrent laryngeal nerve; 8, oesophagus; 9, inferior thyroid artery; 10, common carotid artery; 11, internal jugular vein; 12, trachea.

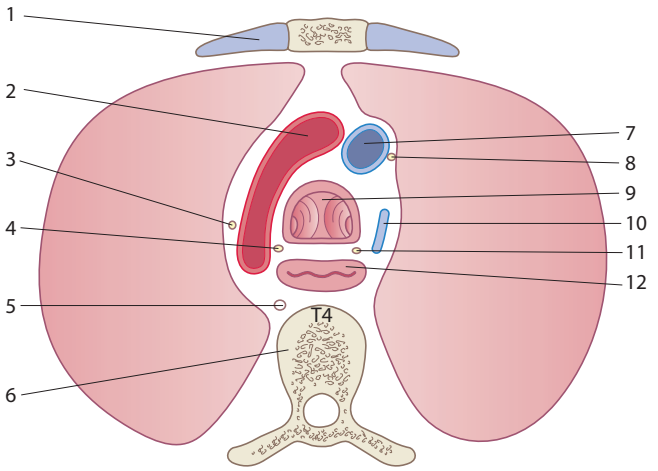

Figure 58.15 Axial section at T4 showing the relationship of the thoracic trachea to surrounding structures. 1, Second costal cartilage; 2, aortic arch; 3, left vagus nerve; 4, left recurrent laryngeal nerve; 5, thoracic duct; 6, fourth thoracic vertebra; 2, superior vena cava; 8, right phrenic nerve; 9, tracheal bifurcation; 10, azygos vein; 11, right vagus nerve; 12, oesophagus.

From anterior to posterior the structures are anterior plexus, pulmonary vessels (artery superior, two veins inferior), bronchi and bronchial vessels, and posterior plexus (**Figure 58.16**). The right side differs from the left as there is an additional upper lobe bronchus lying superiorly. There are lymph nodes and nerves within each hilum.

Anterior to the hilum is the phrenic nerve on the left and the superior vena cava on the right. The descending aorta and left vagus nerve crosses posteriorly to the left hilum, with the right vagus nerve posterior to the right hilum. Superior relations include the aortic arch on the left and azygos vein on the right. Inferiorly a sleeve of pleura hangs down as the pulmonary ligaments and allows movement of the hilar structures.

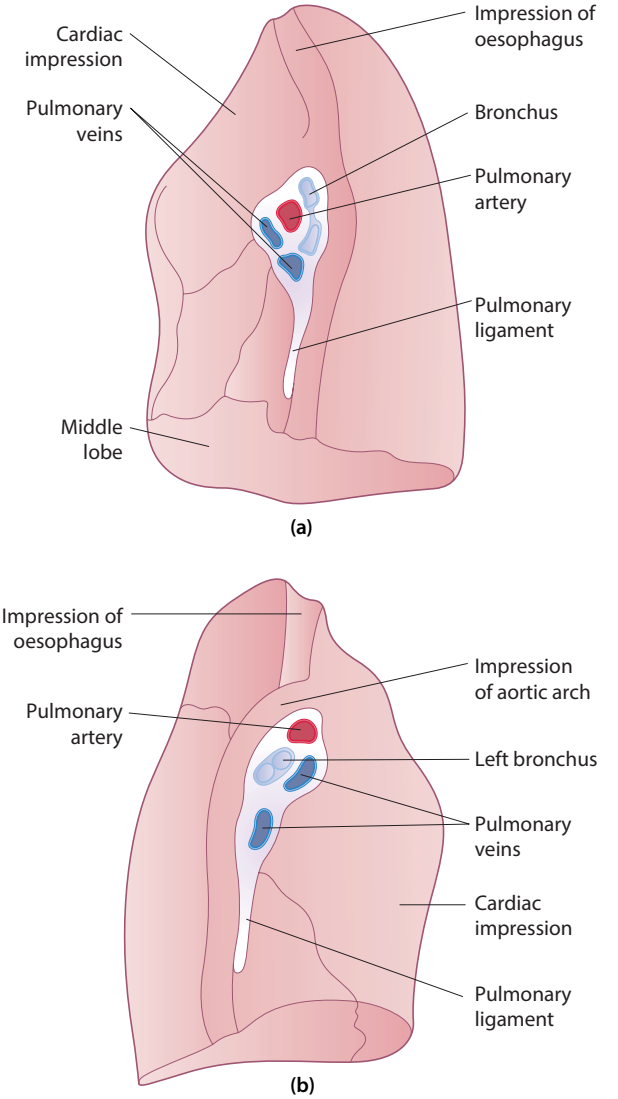

Figure 58.16 Structures in the hilum of the lung: (a) right hilum; **(b)** left hilum.

KEY POINTS

- Minimal swelling in the subglottic larynx can cause severe airway obstruction in infants.
- The pre-epiglottic and paraglottic spaces are connected and allow the unrestricted spread of tumours within the larynx.
- The posterior cricoarytenoid muscle is the only abductor of the vocal cords.
- All the intrinsic muscles of the larynx, except the cricothyroid, are supplied by the recurrent laryngeal nerve.
- The right main bronchus is wider, shorter and more vertical than the left, making it more susceptible to aspiration.

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CHAPTER 59

PHYSIOLOGY OF THE LARYNX

Lesley Mathieson and Paul Carding

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SEARCH STRATEGY

The information in this chapter can be explored more extensively by undertaking a Medline search using the following keywords: voice, larynx, laryngeal physiology, vocal registers, laryngeal innervation, laryngeal mechanoreceptors, neuroanatomy of phonation, biomechanics of phonation, vocal registers, vocal fold vibration.

INTRODUCTION

This chapter is concerned with the functions of the larynx, with particular emphasis on its role as the source of the voice. The motor and sensory laryngeal nerve supply is described and the neuroanatomy of phonation is described in greater detail. A concise section on the role of the larynx in swallowing, coughing and effort closure is followed by a more extensive description of the biomechanics of phonation. It should be noted that it is essential to be familiar with the considerable potential range of laryngeal adjustments that can occur in normal phonation, in order to avoid drawing inappropriate conclusions about phonatory physiology in a clinical setting.

The larynx has a number of functions, the most important of which is to prevent foreign material from entering the airway (aspiration). This is achieved by a combination of heightened sensitivity, a strong sphincteric action during swallowing and a means of effective expulsion (via coughing). The larynx also acts as a valve that can control air pressure and airflow, and as a vibrator for generating sound; both functions are of fundamental importance during breathing, weight bearing and phonation. This chapter is concerned with the neurology and biomechanics of laryngeal functions and lays the foundations for Chapter 60, Voice and speech production.

THE NEUROANATOMY OF PHONATION

Phonation can be defined as a laryngeal motor behaviour used for speech production, which involves a highly specialized coordination of laryngeal and respiratory neuromuscular control.[1] It is dependent upon the integrated functioning of many elements of the central and peripheral nervous systems (CNS and PNS). Although the motor and sensory tracts serving the larynx are relatively well understood, the way in which phonation is initiated and controlled continues to be the subject of neurological research. In addition to the cortical loci associated with voluntary phonation, there is evidence of subcortical representation which is responsible for reflex laryngeal function and involuntary phonation.[2] There is some evidence that the periaqueductal grey matter (PAG), a region of the mid-brain, is a crucial site for mammalian voice production.[3] Not only is it involved in the production of emotional or involuntary sounds but it also appears to generate specific respiratory and laryngeal motor patterns fundamental to human speech and singing. Davis et al. concluded that the patterned muscle activity corresponding to the major categories of voiced and voiceless sound production are represented in the PAG.[3] The role of the PAG might also include integration of cortical and subcortical aspects of language with basic respiratory and

laryngeal motor patterns by which speech is produced.[4–6] The linguistic demands of intonation, phonemic differentiations and emotional nuances in quality would appear to be regulated by such an independent sub-cortical reflex neural system.

The motor activity for vocalization appears to be integrated through a projection from the PAG to a column of neurones known as the nucleus retroambigualis (NRA).[7] The NRA appears to play a significant role in generating respiratory pressure and laryngeal adduction that occurs in both vocalization and vegetative manoeuvres, such as coughing.

Larson[4] suggested that the cortical mechanisms involved in vocalization and speech may have a role in modulating the subcortical systems that are involved in involuntary, or vegetative, phonation such as crying. It is possible that these are the mechanisms for coordinating timing, pitch and intensity fluctuations with the segmental and supra-segmental aspects of speech and voice. There is also evidence arising from clinical cases that the frontal lobes and other cerebral structures are important in the integrated neurological systems required for phonation. Functional magnetic resonance imaging (fMRI) has shown that there is common volitional control of the two upper airway functions of phonation and exhalation.[1] It has also been shown that multiple forebrain systems converge on motor neurones innervating the thyroarytenoid muscle.[8]

The neural pathways for voluntary vocalization arise in the pre-central gyrus of the motor cortex in both cerebral hemispheres and fibres descend as part of the corticobulbar tract, which is part of the pyramidal system or 'direct activation' tract. On reaching the medulla some fibres of the corticobulbar tracts take a direct pathway, remaining on the same side of the body throughout their route. These fibres synapse with the ipsilateral vagus nucleus and subsequently with lower motor neurones without interruption. Other fibres decussate (cross over) and change sides at the bulbar level to synapse with the contralateral vagal nucleus. The vagal nuclei, in the nucleus ambiguus within the reticular formation of the medulla, lie in a group of cells also containing the ninth and eleventh cranial nerve elements. They are influenced by both the pyramidal and extrapyramidal systems.

The indirect neurones of the pyramidal tract have multiple offshoots and synapses with the basal ganglia and reticular formation in the brain stem. They appear to contribute to temporospatial orientation while the direct system is related to discrete movement. The upper motor neurones do not govern isolated muscles, but groups of muscles. The frontobulbar portions of the pyramidal tracts connect with cranial nerves IX–XII, thus controlling articulation, phonation and respiration. The extrapyramidal system refers to tracts other than the pyramidal tracts and includes the basal ganglia in the cerebral hemispheres, the substantia nigra and subthalamic nucleus in the upper brainstem, the cerebellum and the thalamus, among other structures. The basal ganglia consist of the corpus striatum and its associated nuclei, the caudate and lenticular nuclei. The latter is divided into the putamen and the globus pallidus. The cerebellum has an integrating and controlling role over movements that arise in other parts of the motor system. It regulates the force, speed, range, timing and direction of movements throughout the body so that excesses are inhibited. The extrapyramidal system influences the pyramidal tract, the function of which is to regulate the muscle tone required for posture and for changing position. It is also involved in the automatic component of skilled voluntary movement. The specific function of each of these elements of the extrapyramidal system with respect to phonation is unknown but phonation may be influenced adversely by neurological conditions involving these structures.[9]

The extrinsic and intrinsic muscles of the larynx are under voluntary cortical control. They are responsible for the pre-phonatory tuning that precedes phonation and is followed by the phasic, tonic and volitional contractions and also maintenance of length, tension, bulk and position of the vocal folds.[10] The phonatory modulations that take place in speech, however, happen with a precision and speed that suggests a finely coordinated system of reflex controls over the laryngeal muscles themselves, and over the abdominal and intercostal muscles that maintain subglottic air pressure at appropriate levels.[11]

It seems that such fine tuning cannot be cortically regulated.[12] Stimulation of all categories of laryngeal mechanoreceptors initiates activity in the larynx, which presumably ensures that the vocal folds are stabilized and return to their pre-set pattern following displacement by the expiratory air-stream. This process, by monitoring the tonicity and position of the vocal folds, enables necessary adjustments to be made instantaneously and accurately. Although it would seem inevitable that there must ultimately be integration of this feedback system with other control systems during phonation, Wyke[12] and Kirchner[11] stated that this process is independent of auditory feedback.

LARYNGEAL INNERVATION

The vagus nerve (CN X) provides all the innervation to the intrinsic laryngeal muscles and the sensory structures of the larynx. It also supplies the pharynx, palate, trachea, bronchi, lungs, heart, external ear and parts of the gastrointestinal tract. Some of the fibres of the vagus originate in the medulla in the nucleus ambiguus while others originate at a higher level. Cells from the rostral pole of the nucleus ambiguus contain motor neurons for the glossopharyngeal nerve (CN IX), the middle part for the vagus nerve and those from the caudal pole for the accessory nerve (CN XI). The nerve fibres originating in the cranial nerve nuclei form the lower motor neurone pathway. The right and left vagus nerves, which they form, provide ipsilateral innervation to the larynx. The neural 'commands' that travel down to the cranial nerve nuclei are largely responsible for what is ultimately transmitted to the laryngeal muscles via the lower motor neurone pathways. These 'commands' are fashioned by complex interaction of, and constant remodelling by, many cortical, basal ganglia and brainstem influences.

Cranial nerves IX, X and XI are so intimately connected in the medulla that all the muscles supplied by them are frequently involved either equally or progressively in medullary lesions. For this reason, Walshe[13] grouped them together in pathological conditions affecting the nucleus ambiguus in what is termed the 'glossopharyngeal-accessorius complex'. Nuclear lesions of the vagus can be associated, therefore, with paralysis of the palate, tongue and larynx.

The vagus forms a flat cord from its many united filaments and leaves the skull through the jugular foramen, passing vertically down the neck within the carotid sheath. It branches to form the superior laryngeal nerve (SLN), the recurrent laryngeal nerve (RLN) and the pharyngeal nerve:

- The SLN branches off from the vagus at the ganglion nodosum (inferior ganglion), below the level of the jugular foramen, and subdivides into the internal and external SLNs. The internal branch of the SLN consists of both sensory and parasympathetic secreto-motor fibres, which supply glands within the tissue above the level of the vocal folds. This branch of the SLN in turn divides into three branches: (i) the superior branch runs to the lingual surface of the epiglottis and sends small fibres through the epiglottic foramina to the laryngeal surface; (ii) the middle branch runs through the aryepiglottic fold into the ventricular fold; and (iii) the inferior branch runs to the pyriform sinus (or pyriform fossa) and to the postcricoid region, forming various anastomoses with the RLN.[14] The density of nerve endings providing sensory innervation appears to be greatest at the laryngeal inlet as part of the protective mechanism for the respiratory system. The laryngeal surface of the epiglottis has the greatest sensory innervation, while the vocal folds have a lower density of sensory fibres.[15] The anterior vocal folds also have a lower density of sensory receptors than the posterior half. The external branch of the SLN provides the motor supply to the cricothyroid muscle.[14]
- The left and right RLNs provide the motor supply to all the intrinsic laryngeal muscles (see also Chapter 58, Anatomy of the larynx and tracheobronchial tree). The RLNs contain both adductor and abductor fibres.[15] They differ significantly with regard to their origin and pathway. The right RLN arises from the main trunk of the vagus in front of the subclavian artery and the left RLN arises from the vagus at the arch of the aorta round which it winds before ascending to the larynx. Because of its extensive course, the left recurrent nerve is more liable to injury than the right, and is especially vulnerable to pressure from aortic aneurysm and intrathoracic masses. It is also injured during thyroidectomy and thoracic surgery. Therefore, left vocal fold paralysis is far more common than right vocal fold paralysis. The RLNs on both sides ascend the groove between the trachea and oesophagus for a variable distance, before dividing into anterior and posterior branches and entering the larynx behind the cricothyroid articulation.

There is recent evidence that ventricular fold adduction appears to be a result of ventricularis muscle contraction that is mediated by the RLN.[16]

The RLN provides the sensory supply to the glottis and subglottis (see **Figures 59.1** and **59.2**).

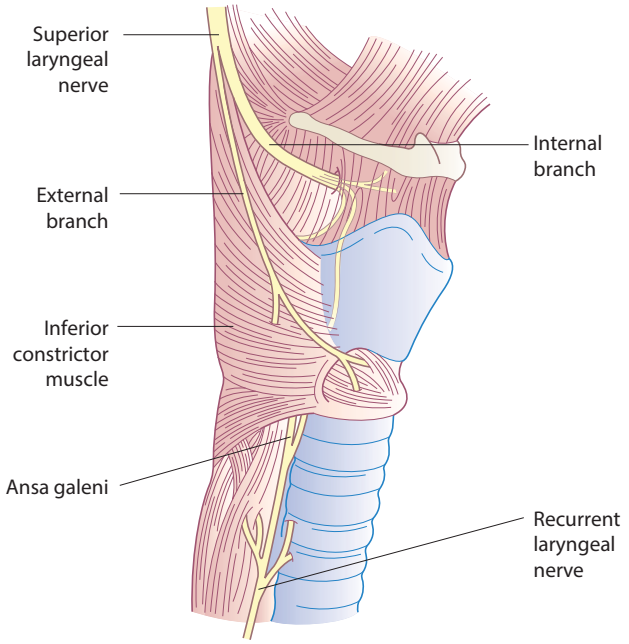

Figure 59.1 Distribution of the recurrent laryngeal nerve (lateral view). Redrawn with permission from Lesley Mathieson.

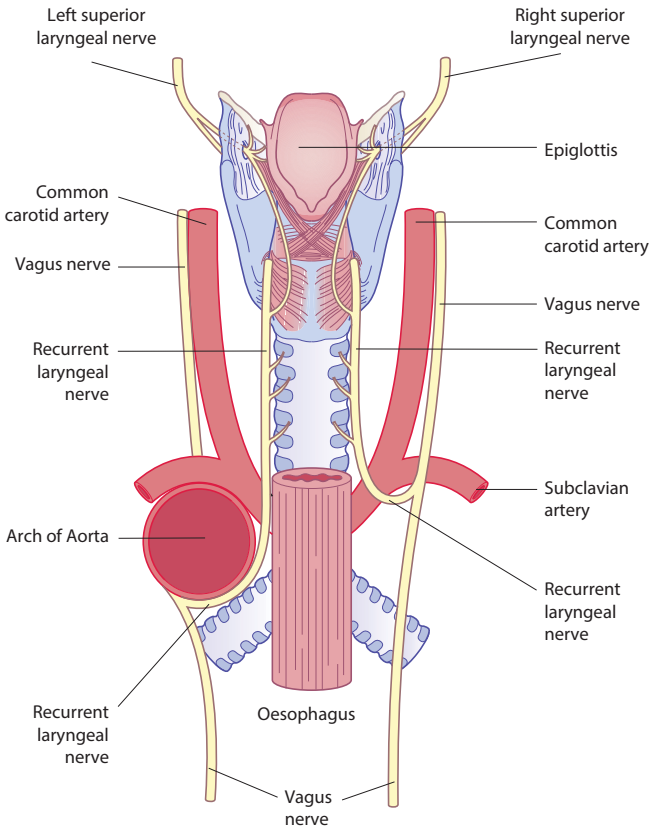

Figure 59.2 Posterior view of the larynx showing the distribution of the left and right laryngeal nerves. Redrawn with permission from Lesley Mathieson.

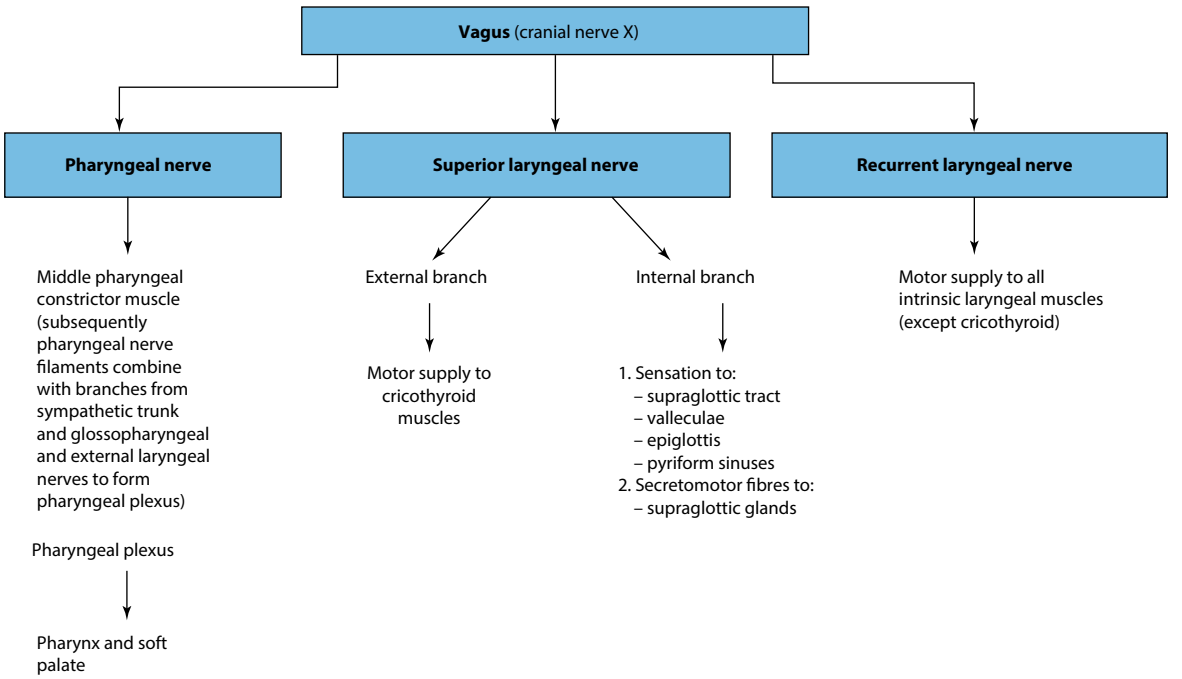

Figure 59.3 Diagrammatic representation of the laryngeal nerve supply. Redrawn with permission from Mathieson.

- The pharyngeal nerve descends between the internal and external carotid arteries to supply the middle pharyngeal constrictor muscle. Its fibres subsequently join with the glossopharyngeal and external laryngeal nerves, together with branches from the sympathetic trunk, to form the pharyngeal plexus. The pharynx and all the muscles of the soft palate, except the tensor palati, are supplied by fibres from the pharyngeal plexus.

Cranial nerves V (trigeminal), Vll (facial), Xll (hypoglossal) and cervical spinal nerves C1–C3 provide the motor supply for the extrinsic laryngeal muscles (see **Figure 59.3**).

Laryngeal mechanoreceptors

Free fibrils and terminal filaments enclosed in capsules constitute the receptor end organs (the mechanoreceptors) embedded in the laryngeal tissues at sites sensitive to muscle stretch and airflow pressures. Some are involved in protecting the airway while others contribute to the control of phonation.[17, 18] Reflex closure of the larynx is triggered by tactile receptors in the glottic and supraglottic mucosa, which evoke reflex contraction of the laryngeal muscles. Similar receptors in the subglottic mucosa elicit laryngeal closure and cough.[11]

Wyke[19, 20] postulated that mechanoreceptors are found in three sites:

1. **The mucosal lining of the larynx (mucosal mechanoreceptors).** The corpuscular nerve endings in the surface covering of the vocal folds are particularly numerous and sensitive to the stimuli of muscle stretch, air pressure level, liquid and touch.[5] They discharge impulses into the afferent fibres of the vagus.
2. **The capsules of the articulatory joints (articular mechanoreceptors).** The existence and function of this group remain controversial.
3. **The extrinsic and laryngeal muscles (myotatic mechanoreceptors).** The tone of the laryngeal muscles depends on the myotatic reflex, which is a function of the muscle spindles. The laryngeal muscles contain a large number of muscle spindles.[21]

FUNCTIONS OF THE LARYNX

Swallowing (deglutition)

During swallowing the primary function of the larynx is to prevent food and liquid entering the airway. This is achieved by means of the sphincteric action of the aryepiglottic folds, the true vocal folds and the ventricular folds, which occurs simultaneously with elevation of the larynx. Laryngeal elevation is also important in controlling pressures and the function of the cricopharyngeal sphincter, in order that the bolus can pass into the oesophagus.[22] The process of swallowing can be divided into the oral stage and the pharyngeal stage. The oral stage is under voluntary control and consists of the oral preparatory stage and the oral transport stage.[23] The food bolus is manipulated by the tongue and broken down before being propelled towards the oropharynx. The pharyngeal stage of swallowing is a reflex activity that is initiated as the bolus reaches the back of the tongue. During this process, the glottis is closed by adduction of the arytenoids and contraction of the lateral cricoarytenoid muscles, false vocal folds and true vocal folds. Vocal fold adduction during swallowing is thought to average approximately 2.3 seconds.[23] The airway is also protected by the epiglottis, which covers the laryngeal entrance and directs the bolus into the valleculae and the

pyriform sinuses. When the bolus arrives at the upper border of the cricopharyngeus muscle, the sphincter relaxes to allow the bolus to enter the oesphageus. An essential feature of normal deglutition is the rapid laryngeal elevation that occurs during the pharyngeal phase of the swallow. This manoeuvre results in the hyoid bone being displaced anteriorly, which further helps to protect the airway from aspiration and also serves to pull open the upper oesophageal sphincter. There is also a drop in pressure and transient negative pressure in the cricopharyngeal sphincter as the bolus passes from the pharynx into the oesophagus. If laryngeal elevation is impaired, then peri-swallow aspiration is more likely, cricopharyngeal opening is limited, the pressure drop during deglutition is slower and the fleeting negative pressure does not occur. A more detailed treatment of swallowing physiology is presented in Chapter 48, Physiology of swallowing.

Coughing

Coughing is the process by which material is expelled from the airway. The laryngeal adductor response is a protective reflex that prevents aspiration. It is preceded by rapid inspiration, followed by forceful closure of both the vocal folds and ventricular folds. Air pressure is then built up below the adducted folds as the diaphragm ascends spasmodically until the folds separate explosively and mucus or foreign material is expelled. This laryngeal motor response to sensory stimuli is not suppressed during volitional laryngeal tasks.[24]

Effort closure

Laryngeal structure has evolved in order to contain intrathoracic pressure, so as to provide a stable fulcrum for the upper limbs. Expiratory effort against a closed glottis is known as the Valsalva manoeuvre.[25] During any form of exertion involving use of the arms, the vocal folds are firmly adducted preventing expulsion of air and collapse of the chest walls, thus providing a fixed origin for the arm and shoulder muscles. This fact is clinically important in that those who have undergone laryngectomy or who have vocal fold paralysis may have difficulty with weight-bearing activities because of their inability to close the glottis effectively. Clinical experience also suggests that trauma to the vocal fold mucosa can occur or be aggravated by forceful, prolonged vocal fold adduction during some types of physical training, such as lifting weights.

Effort closure of the larynx also occurs during childbirth and defaecation as the abdominal contents are compressed by the abdominal muscles in order to achieve expulsion.

The biomechanics of phonation

The vocal folds are composed of laryngeal connective tissues with complex matrix composition and organization that provides the viscoelastic mechanical properties required for producing voice.[26] When the larynx is at rest and respiration is quiet, the vocal folds abduct on inspiration and slightly adduct on expiration. They move up and down slightly in sympathy with the outflow and inflow of respiratory air, while the larynx descends on inspiration and ascends on expiration.[27] The folds are drawn wide apart to a position of full abduction in forceful inspiration. Subglottic and supraglottic influences must be taken into account when analyzing vocal fold dynamics.[28]

INITIATION OF VOICE

Immediately before phonation, the vocal folds rapidly abduct to allow the intake of air. Wyke[20] termed this the 'pre-phonatory inspiratory phase'. Subsequently, the vocal folds are adducted by the contraction of the lateral cricoarytenoid muscles. The vocal note is generated by pulmonary air as it is exhaled between the adducted vocal folds. The vocal folds working together constitute a vibrator, which is activated by the excitor, the exhaled air. The production of the vocal note at this point is the result of the repeated vibratory movement of the vocal folds, known as vocal fold oscillation. The mobility and deformability of the vocal folds determines the ease with which vocal fold vibration can be initiated.[29] Subglottic air pressure increases below the adducted vocal folds until it reaches a level that overcomes their resistance and blows them apart, thus setting in motion the vibratory cycles which result in phonation. The vocal folds, in common with all vibrators, have a degree of inertia, which has to be overcome in order for phonation to occur. The amount of air pressure required to begin voicing is known as the 'phonation threshold pressure'.[30] The size and tension of the vocal folds in combination with the viscoelastic properties of the vocal fold cover will affect the phonation threshold pressure.[29]

THE VIBRATORY CYCLE

Each vibratory cycle of the vocal folds consists of three phases: adduction, aerodynamic separation and recoil (**Figure 59.4**). As the increased subglottic air pressure overcomes the resistance of the adducted vocal folds at the onset of phonation, the vocal folds peel apart from their inferior border. When they finally separate at their superior margin, a puff of air is released. The resulting negative pressure in the glottis caused by the Bernoulli effect results in the vocal folds closing rapidly as they are sucked together, the inferior vocal fold margins closing first. The Bernouilli effect is a drop in pressure dependent on particle velocity. In relation to the vocal tract, Maran[31] described it as follows: 'When air passes from one large space to another (e.g. from lung to pharynx), through a constriction (the glottis), the velocity will be greatest and the pressure least at the site of the constriction.' As a result of the drop in pressure at the glottis, the vocal fold mucosa is drawn into the space between the vocal folds.

Contact between the vocal folds increases until the subglottic air pressure is high enough to blow the vocal folds apart again, and the cycle recommences. Each cycle of adduction, separation and recoil is the manifestation of a mucosal wave travelling from the inferior to the superior surface of each vocal fold. The process by which this undulating wave of movement of the mucous membrane

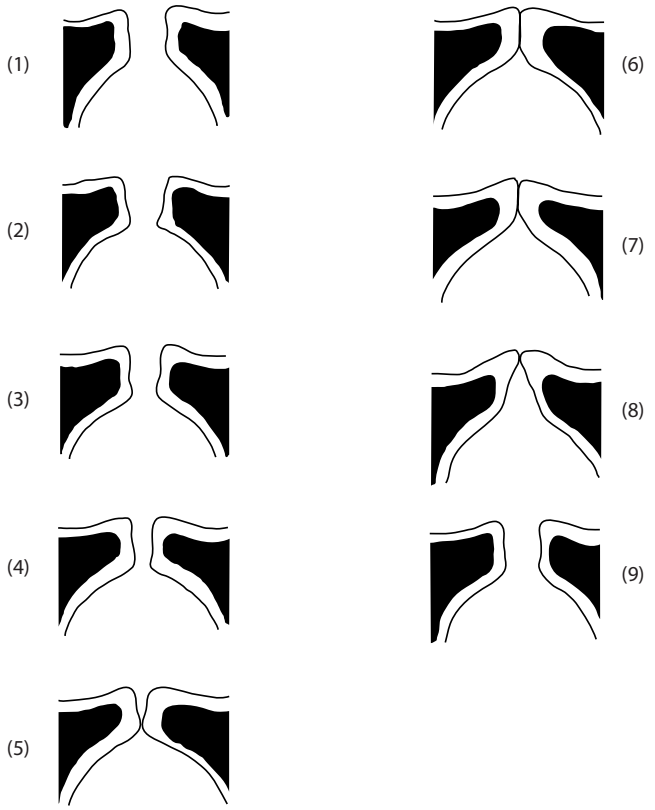

Figure 59.4 Vocal fold vibratory cycle. Redrawn with permission from Mathieson.

occurs is dependent on what is known as the cover/body theory. That is, the vocalis muscle provides the firm body of the vocal fold over which the mucous membrane cover of the vocal fold is blown by the expiratory air stream. These undulations of the vocal folds' thin cover, and any abnormalities of the mucosal wave, can only be observed using laryngostroboscopy or high-speed photography.[32]

The periods of vocal fold contact and lack of contact in one vibratory cycle can be divided broadly into closed and open phases, respectively, with associated closing and opening phases.[33] The closing phase of the vocal folds is more rapid than the opening phase. The phases of the vibratory cycle can be classified, therefore, into four stages as shown in **Box 59.1**.

The vocal folds have to be structurally and functionally symmetrical, at the same level, and close rapidly in order that a clear vocal note can be initiated and maintained.[34] Insufficient approximation of the vocal folds (glottal insufficiency) results in air wastage and production of a breathy voice quality. When the vocal folds fail to approximate completely along their membranous portion, with a slightly increased aperture in the cartilaginous section, turbulent air escapes and is audible in the voice.

BOX 59.1 The periods of vocal fold contact and lack of contact in one vibratory cycle

Closing phase: The vocal folds begin to close rapidly from their lower margin

Closed phase: The medial edges of the vocal folds are in full contact

Opening phase: The vocal folds begin to separate from their lower margin and gradually peel apart. The superior margin remains in contact until the end of this phase.

Open phase: The vocal folds are separated. (The longest part of a normal vibratory cycle.)

Reproduced with permission from Mathieson.

In production of notes of middle pitch, the interarytenoid muscles adduct the cartilaginous portion of both vocal folds and hold them together while the anterior portion of each fold is gently adducted but free to vibrate in the expiratory airflow. Although full vocal fold adduction during phonation has traditionally been regarded as the norm, clinical observation and various studies have refuted this view by showing that normal phonation can occur when there is incomplete glottal closure.[35, 36] This pattern of vocal fold adduction is more common in women than in men. In all speakers, incomplete glottal closure can be considered normal in high frequency modal voice and in falsetto (see **Figure 59.5**), when hourglass or spindle glottal configurations can occur in normal subjects.[37] It also appears that different types of glottal configurations are associated with different age groups. Incomplete closure of the posterior part of the vocal folds (posterior glottal chink) is a common finding in young and middle aged women, but elderly women are more likely to exhibit anterior chinks.[35, 38] High-speed digital imaging has revealed that glottal configuration and phase closure for children with normal voices are distinctly different from those of adults. It has been suggested that posterior glottal gap and a predominantly open phase of the glottal cycle should be considered as normal glottal configuration in children during modal pitch and loudness.[39] It is essential, therefore, that clinicians dealing with vocal pathology recognise that incomplete vocal fold closure may be a normal glottal configuration during phonation in certain subjects and at certain frequencies. Similarly, asymmetries within the larynx should be viewed with caution as they are not necessarily indicative of pathology. For example, a lack of strong differences in the prevalence of arytenoid asymmetries in the adducted position have been found in speakers with and without voice disorders.[40]

Age-related changes to the vocal tract can give rise to vocal instabilities in non-pathological voices. Changes in pitch and breath rate in older individuals indicate a fundamental change in the body's maintenance of the speech mechanism.[41] Reductions in pulmonary elastic recoil and respiratory muscle strength can affect the way in which older adults generate subglottal air pressure required for speech production. They have been shown, for example, to have very different lung volume adjustments for loud speech, compared to young adults.[42]

VOCAL REGISTERS: CHARACTERISTICS OF VOCAL FOLD ADDUCTION AND VIBRATION

Significant variations in vocal fold vibratory characteristics and adduction can also be observed according to

the vocal register that is being used. The subject of vocal registers is confusing and controversial. This is partly because the definition of what constitutes a register has been unclear but also because a number of terms are used to describe each register. Traditionally, registers have been regarded as the perceptually distinct regions of vocal quality over certain ranges of pitch and loudness[32] but listener identification of the change from one register to another is not reliable.[43] The terms used vary according to whether they are being employed by singers or speech scientists, but even then their use is not uniform. Singers tend to classify the registers as head, middle and chest but these terms are regarded as unsatisfactory by voice scientists, many of whom refer to three main vocal registers: falsetto, modal and vocal fry. These classifications, however, do not relate directly to each other. Baken and Orlikoff[44] noted that the problems of definition and terminology had been clarified by Hollien's suggestion[45] that registers should be defined in terms of laryngeal behaviour, rather than in acoustic terms, as registers are governed by the degree of contraction of the vocalis muscle. As a result, the terms loft, modal and pulse registers can be used with less confusion; they describe the vibratory pattern of the vocal folds and the acoustic parameters being produced (see **Table 59.1**):[46]

- **Loft register (or falsetto)** covers the highest frequencies of the voice. The vocal folds are lengthened, extremely tense and thinned so that there is minimal vibration. The knife-thin free edges are almost adducted and subglottic air pressure is high. During the production of these high frequencies, the larynx is raised by the suprahyoid muscles and the pharynx is shortened.[47]
- **Modal register** encompasses the range of frequencies usually employed in speech and singing. The membranous portions of the vocal folds are adducted and make complete closure in the closed phase of each vibratory cycle. In cross-section, the vocal folds are triangular in shape. In low notes the intrinsic muscles relax, the folds increase in bulk and their opposing surfaces deepen from 3 mm to 5 mm. They vibrate slowly along their whole length, the lower surfaces of their 'lips' making contact and separating as the upper surfaces approximate in a rolling motion or figure of eight. In lowest notes the infrahyoid muscles pull the larynx down.[48]
- **Pulse register (or glottal fry or vocal fry or creaky voice)** occurs during the lowest vocal frequencies and is a feature of normal speech.[49] This terminology reflects the pulsatile nature of the laryngeal sound generated. There is a long closed phased in each vibratory cycle.

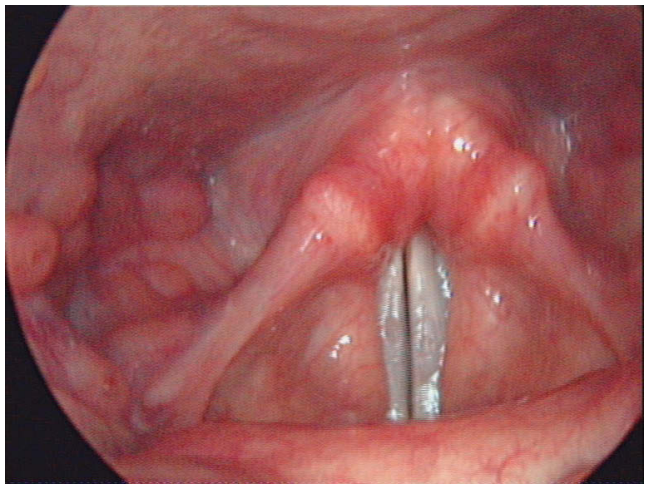

Figure 59.5 Normal falsetto phonation.

The terminology and underlying modes of vocal fold behaviour during the production of each register are outlined in **Table 59.1.**

Appreciation of the normal patterns of vocal fold movement and the way in which laryngeal adjustments affect the sound of the voice is essential to evaluating laryngeal findings in cases of disordered voice. Considerable variations of structure and function can be found even in the normal larynx and there are probably even more permutations of laryngeal behaviour. A comprehensive range of vocal tasks throughout the patient's pitch range during laryngoscopic examination is essential, therefore, if inappropriate conclusions regarding laryngeal pathology are to be avoided.

TABLE 59.1 Vocal registers

	Register may include	Equivalent terms	Vocal folds	F0 range (Hz)
Loft register	Highest vocal frequencies	Falsetto	Thin, tense, lengthened. Minimal vibration	275–1100
Modal register	Range of fundamental frequencies most commonly used in speaking and singing	Chest, head, middle, heavy voice	Complete adduction	100–300
Pulse register	Lowest range of vocal frequencies: laryngeal output is perceived as pulsatile	Vocal fry, glottal fry, creaky voice	Long closed phase	20–60

The terminology related to vocal registers is not consistent. Various overlapping terms are used that have different theoretical bases.

FUTURE RESEARCH

- Detailed innervation of the laryngeal structure.
- The processes of regulation of the linguistic demands of intonation and emotional nuances in vocal quality.
- The cerebral systems controlling phonation.
- Studies of normal variations of the vocal tract during phonation.

KEY POINTS

- The prime function of the larynx is to protect the airway. It also acts as a valve controlling airflow and air pressure and as a vibrator for generating sound (voice).
- The vagus nerve (CN X) provides all the innervation to the intrinsic laryngeal muscles and to the sensory structures of the larynx.
- Phonation involves highly specialized coordination of laryngeal and respiratory neuromuscular control.
- The quality of the glottal source sound is dependent on the structure and function, particularly the efficiency of approximation, of the vocal folds.
- An understanding of normal and age-related differences of glottal configurations is essential in order to avoid pathologizing normal laryngeal structure and function.

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CHAPTER 60

VOICE AND SPEECH PRODUCTION

Paul Carding and Lesley Mathieson

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SEARCH STRATEGY

Data in this chapter can be explored more extensively by undertaking a Medline search using the following keywords: speech, voice, articulation, larynx, phonatory biomechanics, vocal fold vibration, vocal registers, intonation, phonetics and paralinguistic features.

INTRODUCTION

This chapter outlines how humans produce speech and voice. The characteristics of the glottal source (vocal fold vibration) are described. How the sound is modified within the oral tract is then addressed in detail. This is followed by a brief explanation of the fundamental principles of speech and articulation. Finally, the importance of the paralinguistic features of voice and speech are described.

The vibration of the vocal folds ('phonation') constitutes the raw glottal sound source. However, the voice we hear is far more complex than the acoustic signal generated by the vibrating larynx. This fundamental vibratory sound is modified and resonated by the rest of the vocal tract to produce a recognizable human voice quality. Hence, analysis of voice quality (perceptual or instrumental) must recognize the role of the whole vocal tract in the production of the sound that finally radiates from the mouth. Furthermore, the articulatory structures of the vocal tract (lips, tongue and soft palate) shape the sound source in an infinite number of combinations to make speech. This co-ordination of phonatory and articulatory behaviours represents arguably the most advanced sensorimotor system to be found in the human body.[1] Speech and voice require precise co-ordination of reflexive and learned behaviours resulting in intricate muscle movements executed with accuracy and speed. The flexibility of the vocal tract and the anatomical variations between people allows for an enormous range of normal voice and speech qualities and an inevitable overlap between 'normal' and 'abnormal' parameters. This has implications for how we assess and measure components of speech and voice for diagnostic and outcome evaluation purposes.[2] The main features of human voice and speech production are described in more detail below.

The specific characteristics of an individual's speech and voice are the product of the organic and phonetic features of the speaker.[3] Organic factors are derived from the nature of the speaker's individual anatomical apparatus; the dimensions and geometry of the nasal and oral structures, pharynx, larynx and respiratory system. Phonetic features refer to the speaker's habitual muscular adjustments of the speaking apparatus in terms of long term muscle 'settings' (for example, larynx position or tongue body position). The specific anatomical configuration of the vocal tract is unique to each individual and produces a voice and speech quality that distinguishes one speaker from another. These phonetic muscular habitual settings are learned (often unconscious) behaviours that fulfil the speaker's social, geographical, cultural and personal needs.

CHARACTERISTICS OF THE SOUND SOURCE/GLOTTAL SIGNAL

Voice quality

The quality of the vocal sound source is wholly dependent upon the vibratory characteristics of the laryngeal structures.[4] More specifically, it is dependent upon the

nature of vocal fold adduction during phonation and the regularity of the mucosal waves of the lamina propria (see Chapter 59, Physiology of the larynx). However, regular ('periodic') vocal fold behaviour also requires a stable airflow to generate vibration of the laryngeal structures.

- Incomplete adduction of the vocal folds during phonation will commonly result in audible air leakage and a 'breathy' voice quality. Whisper occurs when there is insufficient vocal fold adduction to achieve vibration but sufficient adduction to produce audible turbulent air. It is also associated with an increase in infra-glottic airflow.
- An irregular mucosal waveform vibration will result in an aperiodic sound that will be perceived as 'hoarse'. There are many possible causes of irregular laryngeal vibration, including inflammation, focal lesions and muscle imbalance.
- A pressed or strained voice quality occurs when the vocal folds are strongly adducted (often with supraglottic muscular involvement) and there is raised subglottal air pressure.
- It is quite possible for several aspects of suboptimal vibration to co-occur and hence produce a complex voice quality of more than one aberrant feature.

In a hypothetically perfectly functioning larynx, adduction of the vocal folds would be complete during the closed phase of phonation and abduction would be smooth and quick (in order to start the closing phase of the next vibratory cycle). Furthermore, each vibration of the mucosal waveform would be identical to the previous one and the sound signal produced would be perfectly periodic (a sine wave). The sound thus produced would contain only a fundamental frequency and its harmonics. However, all human voices are a combination of periodic and aperiodic sound. Aperiodic sound or 'noise' is a sound that is not a harmonic of the glottal signal. The main sources of 'noise' in the larynx are air escape and irregular vibration.[2] The more severe the noise component of the sound (in relation to the periodic component), the more 'hoarse' the voice will sound.[2, 5] It is possible to measure the degree of 'hoarseness' in a voice by calculating the ratio of periodic sound compared to aperiodic sound. This is usually termed a 'harmonics-to-noise ratio' (HNR).[5] It is important to note that the acoustic HNR measurement provides some indication of the degree of hoarseness but no information as to the source of the noise component.[4] HNR measurement has become a popular measure of dysphonic severity and of change in voice quality during treatment.[2]

Voice frequency

The frequency of the glottal signal is a result of the number of vibratory cycles per second (measured in hertz). The rate of vibration of the vocal folds is a function of the vocal fold length, elasticity, tension and mass, and their subsequent resistance to subglottal air pressure.[4] The maintenance of a steady vocal frequency requires control of all of these interacting physiological features. Frequency increases with a lengthening of the vocal folds and the subsequent thinning and stiffening of the vocalis muscles.[6] The perceptual correlate of frequency is pitch although the relationship between the two is a complex one. The frequency, intensity and spectral properties of a sound interact in very complex ways to lead to a given pitch perception.[5] Considerable normative data of habitual speaking pitch or mean speaking fundamental frequency (MSFo) exists.[5] However, there is a huge range of what is considered 'normal' depending on the age, sex, emotional state, communicative intent, mood and personality of the speaker. Similarly there are data on vocal pitch range both in terms of maximum range and habitual speaking range.[5] It is generally accepted that there are three pitch registers: loft (or falsetto) register; modal (or middle) register; and pulse (or chest) register (see Chapter 59, Physiology of the larynx). These registers basically distinguish between different vibratory patterns of the vocal folds determined by the degree of contraction of the vocalis muscles.[7] Short-term (cycle-to-cycle) variance in the frequency of vocal fold vibration is called 'jitter' or pitch perturbation. In a speaker who is trying to maintain a stable pitch, a measurement of jitter may indicate instability in the phonatory mechanism and may be a further useful index of dysphonia.[2, 5]

Voice amplitude

Vocal loudness is the perceptual correlate of amplitude – the size of the oscillation of the vocal folds. The amplitude of these vibrations is largely determined by the force of the transglottal airflow. Increasing both the airflow through the larynx and vocal fold resistance (and subsequent subglottal pressure) will result in an increase in vocal loudness. Like vocal frequency there are data on normal vocal intensity (habitual and range) in a variety of settings.[5] Short-term variance in the intensity of the vocal signal is called 'shimmer' or amplitude perturbation. An inability to maintain stable amplitude when intended may indicate important characteristics of the dysphonic speaker.[2, 5]

MODIFYING THE GLOTTAL SIGNAL

The sound source produced by the vibrating vocal folds is modified by the rest of the vocal tract to produce the voice quality that radiates from the speaker's mouth to the listener's ear. In a normal voice, the glottal signal is essentially periodic and composed of a fundamental frequency and its harmonics. This complex acoustic signal is then filtered by the supralaryngeal tract with some anatomical structures resonating different harmonics of the source signal more than others. Changes in the shape of the whole vocal tract (and the dimensions of the oral, nasal, pharyngeal and laryngeal cavities relative to each other) can be achieved in numerous ways. For example, protruding the lips, retracting the tongue base, lowering the larynx or lowering the soft palate will all dramatically alter the sound of the resultant voice even when performed in isolation. The fact that the voice is more than its vibratory

source is a fundamental principle of auditory evaluation of voice quality.[2, 8] It is important to note that some voice quality rating scales concentrate on laryngeal vibratory features only (i.e. the grade, roughness, breathiness, asthenia, strain (GRBAS) scale) whilst others take into account distinguishing perceptual features of the whole vocal tract (i.e. the Vocal Profile Analysis Scheme).[8] The modification of the sound source by the supraglottic vocal tract also represents the main problem in the instrumental measurement of voice quality. For this reason most methods of acoustic analysis prefer to analyze 'steady-state' prolonged vowels where the speaker is attempting to maintain steady pitch and intensity and where the variance in supralaryngeal tract configurations is kept to a minimum.[2, 5]

VOCAL RESONANCE

As explained above, the supralaryngeal tract acts as a resonating chamber for the complex acoustic signal generated by the vibrating vocal folds. The specific geometry and dimensions of an individual speaker's vocal tract will determine the 'timbre' or resonating properties of the voice. Skilled speakers and singers learn to manipulate these oral, nasal and pharyngeal structures to maximize their resonant properties. This is not easy to do since vocal resonance changes continually as we speak (i.e. changing vocal pitch or intensity, articulating different consonants or vowels). Oral resonance is affected by the degree of jaw movement, mouth opening, tongue body raising and pharyngeal constriction. Nasal resonance is affected by excessive or limited action of the velopharyngeal sphincter during speech, or by some degree of nasal obstruction. For a majority of normal speech the velopharyngeal sphincter is closed; the diaphragm of the velum reflects most of the sound into the oral cavity. However, some speech sounds require significant resonation into the nasal cavity (i.e. m, n and ng sounds). The final result is a voice with an appropriate oral/nasal balance. Appropriate oral/nasal resonance is not only necessary for normal sounding speech and voice but is also important to facilitate good voice projection (by enhancing the fundamental frequency and its harmonics).[9]

Velopharyngeal incompetence or significant lowering of the soft palate will result in a hypernasal speech quality. In more extreme cases, audible nasal air escape can be heard during speech. There is evidence to suggest that listeners tend to associate negative personal attributes to individuals with hypernasal speech.[10] Structural abnormalities such as a cleft palate or submucosal cleft often result in marked hypernasality. Conversely, an inability to produce appropriate nasal resonance (especially for sounds m, n and ng) will result in hyponasal speech quality. This is, of course, most likely to occur in space-occupying conditions of the nasopharynx. Removal of the space-occupying lesion or tissue may result in hypernasality although this is likely to be temporary in most cases. A significant but poorly investigated possible complication of the uvulopalatopharyngoplasty (UPP) surgical procedure is the resultant hypernasal speech.[11]

FUNDAMENTALS OF SPEECH/ ARTICULATION

Orchestrated movements of the organs of articulation change the vocal sound into recognizable speech. This process is often called the 'source-filter' model of voice production.[12] These articulatory movements can be classified as vowels or consonants (although the actual distinction between the two is theoretically complex). In simple terms, vowels are sounds in which there is no obstruction to the flow of air as it passes from the larynx to the lips. Consonants require a more definite obstruction by one or more of the articulators in the oral tract. This distinction becomes less useful for sounds such as 'w' or 'y', which we call consonants but are in reality articulated like vowels. For this reason these sounds are commonly called 'semi-vowels'.[13, 14]

All vowel sounds are continuants (i.e. they have length of varying periods of time). For practical purposes it is sufficient to differentiate between short vowels (i.e. p**i**t) and long vowels (i.e. p**ar**t). In a diphthong, two vowel sounds are combined (i.e. f**ire**). Vowel articulations are made by varying the resonating shape of the oral and pharyngeal cavities.

Changing the shape of the vocal tract subsequently changes its resonating behaviour; different shapes responding to different components of the harmonic structure of the glottal sound source. The resonance peaks of the vocal tract are called formants. These formant structures vary for each vowel and are easily identifiable on a sound spectrograph.[5] It is possible to distinguish between vowels by changing (i) the height of the tongue raising in the mouth, (ii) the part of the tongue which is raised (front, centre, back) and (iii) the position of the lips (spread or rounded). For example, the vowel /i:/ as in '**see**' is made with the front of the tongue raised and with lips spread. In contrast, the vowel /u:/ as in '**sue**' is made with back tongue raising and rounded lips. Diphthongs (i.e. '**beer**', '**air**') start with one oral tract articulatory shaping and glide to another.

Speech consonants are defined by their much clearer articulation (and often obstruction of the airflow) within the oral tract. Distinction between consonants can be made using three main elements: the place of articulation (i.e. lips, alveolar); the manner of articulation (i.e. plosive, fricative); and the state of the larynx (voiced or voiceless). All of these elements require further explanation.

The place of articulation

Consonants are clearly articulated at different places within the oral tract. Bi-labial consonants refer to articulation between the upper and lower lips (p, b, m, w). Labio-dental consonants require top teeth and lower lip articulation (f, v). Dental articulation refers to tongue tip and top teeth occlusion (th). Alveolar consonants are made by the tongue tip touching the ridge behind the teeth (t, d, n, s, z, r, ch, dj). Articulation of the middle tongue with the hard palate produces 'y'. Velar consonants require back of tongue and soft palate articulation (k, g, ng). See **Table 60.1** for a complete list of standard English consonants.

TABLE 60.1 Standard English consonants

	Bi-labial	Labio-dental	Dental	Alveolar	Palatal	Velar	Glottal
Plosive	p **b**			t **d**		k **g**	
Fricative		f **v**	Th[i] **th**[ii]	s **z** sh **jz**[iii]			
Affricate				ch **dj**[iv]			
Nasal	**M**			**n**		**ng**[v]	
Approximant	**W**			**l r**	**Y**		**H**

Bold signifies voiced; [i] as in 'th ink'; [ii] as in 'th at'; [iii] as in 'mea s ure'; [iv] as in 'j aw'; [v] as in 'si ng'.

The manner of articulation

The manner of consonant articulation refers to how the airflow is obstructed in the oral tract. Traditionally these are split into five categories: plosives, fricatives, affricates, nasals and approximants.

English has six plosive consonants: /p, b, t, d, k, g/. These plosives have different places of articulation (see previous section and **Table 60.1**). In all cases one articulator is moved against another in order to completely interrupt the airflow through the vocal tract. The air is temporarily compressed behind the point of articulation and then released with an audible noise called 'plosion'.

In contrast, fricatives are continuant consonants (they can continue for a relatively long time). The main characteristic of fricatives is the air turbulent sound that is made by air 'hissing' through the close (but not complete) approximation of two articulators. Like plosives, fricatives have different places of articulation (see **Table 60.1**). Examples of English fricatives include f, z, and s.

Affricates are a combination of plosion and fricative articulation. A common example is the affricate consonant heard at the beginning and end of the word 'church'. It begins with the plosive t and then the tongue moves to the position for the fricative sh. The plosive is followed immediately by the fricative noise but is heard as one consonant sound. There are only two affricate sounds in English (ch and dj, as in the beginning and ending sounds in 'church' and 'judge'), and both are articulated with the tongue tip and alveolar.

The basic characteristic of the nasal consonants (m, n, ng) is that air escapes through the nose. The air is prevented from passing through the mouth by obstructive lip or tongue articulation and the soft palate is lowered to allow nasal air escape. The soft palate is raised for all other standard consonants and vowels. Inadequate velopharyngeal competence will result in inappropriate 'nasalization' of non-nasal consonants and vowels. Permanent obstruction in the nasopharynx and lower nasal passages will result in 'denasalization' of nasal consonants.

Approximant consonants occur when the articulators are not sufficiently close to produce 'complete' consonants such as plosives, fricatives or nasals. Again, place of articulation can vary (see **Table 60.1**). These consonants are articulated similarly to vowels and are therefore often called semi-vowels. English examples of approximants include w and y. The lateral approximant 'l' varies slightly since the passage of air escapes along the sides of the tongue.

The state of the larynx

Finally, consonants can be either 'voiced' or 'voiceless'. A number of consonants can be 'paired', where the only difference between them is whether their articulation is accompanied by voicing or not (i.e. p and b, t and d, k and g, s and z). The place and manner for both members of each pair is the same. The only difference is that the first in each pair is 'voiceless' – there is no vibration of the vocal folds for the split second that these consonants are being articulated. The voiceless consonant 'h' does not have a voiced twin in standard English. This means that in connected speech, vocalization is not continuous. Phonation is switched on and off (for milliseconds of time) to signal voiceless consonants. This extremely subtle phonatory timing is crucial for intelligible speech and is a characteristic problem of some dysphonic voices. In **Table 60.1** the voiced consonants are signalled by **bold** type.

PHONEMES, ALLOPHONES, PHONOLOGY AND LANGUAGE VARIANCE

Phonetics is the study of speech sounds and how the rules of language organize and change sounds in different contexts.[13, 14] The consonant and vowel articulation described in the previous section is theoretically accurate but, in reality, can be modified and varied on an almost infinite level. Any speech sound (or phoneme) may be articulated slightly differently according to the other sounds around it. These variations of the same phoneme are called 'allophones'. For example, the sound 't' in the words 'tea' and 'tree' are, in fact, articulated with a slightly different tongue position. This is one reason why simulated (computerized) speech does not sound natural. In more extreme cases, speech sounds may change altogether depending on their phonetic environment or even be omitted altogether. For example, consider how 'handbag' is regularly pronounced 'ha**m**bag' and 'nightmare' is pronounced 'nigh'mare'.

Phonology is the sound patterns of a particular language. The way children develop the phonology of the language is well understood[15] and the differentiation between development phonological deviance as opposed to phonological delay is an important clinical consideration.[15] Clearly, different languages have different phonological sets and therefore will include some consonants and vowels that may not feature in English speaking at all.

PARALINGUISTIC FEATURES OF VOICE AND SPEECH

Speech and voice are more than just the products of muscular movements. For example, they represent an immensely powerful (and efficient) means of conveying mood, personality and intent. Our speech and voice also provides messages about our education, social status, emotional state and personality. All of these things are interpreted from the way the speaker uses features such as speech rhythm, speech rate, vocal intonation, vocal tone or quality and voice loudness. 'Everything is said in a certain way, in a certain tone of voice and at certain loudness.'[4] However, it is rare for a speaker to be using these features consciously (unless the speaker is an actor). The unconscious use of these paralinguistic features may be more revealing than the speaker anticipated and more enlightening than the language content of what is being spoken. It is partly for these reasons that voice or speech impairment may result in severe levels of personal handicap, disability and distress.[16, 17]

Speech rhythm is learned as an integral part of early childhood speech, voice, language and communication development. Early babbling is a 'working vocal guidance system … in which the ear monitors vocal tract activity and informs speech-motor control systems about targets and adjustments needed for mimicry of ambient speech'.[18] Speech rhythm is language- and even accent-specific. Speech rhythm (and stress) is one of the most difficult linguistic features for foreign speakers to master and will distinguish them from truly bilingual speakers who were exposed to several speech rhythm patterns from birth.[19] To complicate the matter further, regional accents often demand different speech rhythms again. For example, it may be possible to identify locals from Newcastle simply by how they stress the syllables in the word 'Newcastle'. Locals will stress the second syllable (New**castle**) whereas most other speakers will naturally stress the first syllable (**New**castle). Finally, loss of rhythm and incorrect stress may render speech almost unintelligible even when articulation and voice production are normal.[4]

Speech rate is often interpreted as an indicator of anxiety (if it is too fast) or low intellect (if it is too slow).[20] Our speech rate is also likely to reflect our state of arousal (excited, drowsy, stressed etc.) and is clearly linked to other physiological systems such as pulse and respiratory rate.

Vocal intonation refers to the use of varying vocal pitch to indicate various grammatical, psychosocial and semantic features. We use intonation to indicate communicative intent (e.g. to characterize a question or to indicate certainty in a statement) and to manipulate conversation (e.g. to encourage a response). Patterns of intonation are often used unconsciously by the speaker and are, of course, open to misinterpretation by the listener. Similarly, the pitch range used by a speaker may reflect emotional status. A wide frequency range indicates arousal in contrast to a narrow ('flatter') range, which may be interpreted as sadness or impassiveness.[21] Habitually low pitch may indicate depression and high pitch may suggest anxiety.[22] A clear understanding of the components of phonatory behaviour (e.g. laryngeal muscle tone, pulmonary airflow, subglottal pressure, supralaryngeal tension) provides a physiological explanation for these paralinguistic features of voice.

The emotional content of a verbal message is also likely to be reflected in changes in vocal tone or quality.[23, 24] These result from changes in laryngeal and supralaryngeal tension, which in turn affect vocal features. For example, a breathy vocal quality may indicate anxiety[25] or vulnerability[26] and may be interpreted as revealing lower social class, especially when associated with harshness.[27] Conversely, vocal creak (low pitched, irregular vocal fold vibrations) may indicate a relaxed state and has been shown, at least in one study, to correlate with higher social status.[27] Vocal loudness appears to be different between the sexes even when the context and linguistic content are similar: men talk more loudly than women.[27] Not surprisingly, we commonly associate vocal loudness with confidence and extrovert personality but inappropriate loudness may indicate insensitivity and poor pragmatic skills.[28] Clearly, the interpretation of a speaker's vocal quality and volume are, like all other paralinguistic features, subjective and may subsequently result in misunderstandings.

Almost all paralinguistic aspects of speech and voice are intuitively known but not consciously learned (or manipulated). They contribute as much to our individual speech and voice characteristics as our specific anatomical configurations and habitual vocal settings. These paralinguistic features of speech and voice remain a crucial aspect of speech and voice production and help to explain why many people with a speech and voice disorder report severe personal, social and economic consequences.

FUTURE RESEARCH

- Cultural differences in speech and voice and the importance of these differences on non-organic voice pathology.
- The impact on voice and speech disorders on tonal languages.
- Closer mapping of acoustic and physiological measurement to the auditory features of speech and voice.
- Development of a reliable and practical auditory perceptual rating scale for supraglottic features of voice quality.
- The application of the analysis of paralinguistic features of speech and voice in psychiatric and psychological differential diagnosis.

KEY POINTS

- The voice is the product of vibrating vocal folds and sound resonance throughout the vocal tract.
- The specific characteristics of an individual's speech and voice are the product of the organic and phonetic features of the speaker.
- The quality of the glottal sound is wholly dependent upon the vibratory characteristics of the laryngeal structures.
- Orchestrated movements of the organs of articulation modify the vocal sound into recognizable speech.
- Paralinguistic features of voice and speech include speech rhythm, stress, accent and vocal intonation.

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CHAPTER 61

ASSESSMENT AND EXAMINATION OF THE LARYNX

Jean-Pierre Jeannon and Enyinnaya Ofo

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SEARCH STRATEGY

Data in this chapter are based on Medline, PubMed, hand searches and the Cochrane review database using the keywords: larynx, clinical examination, adult, paediatric, laryngoscopy, endoscopes, optical imaging and difficult airway.

INTRODUCTION

The purpose of the chapter is to review the techniques available for accurate and safe examination and assessment of the upper respiratory tract. The otolaryngologist must have a systematic method to process symptoms and signs in order to achieve the correct diagnosis.

ASSESSMENT IN THE CLINIC

Evaluation of the patient begins as soon as he/she enters the clinic room. Preliminary assessment of their respiratory status can be made during history taking. The patient with respiratory distress may be unable to speak a few words before needing to rest, whereas a healthy individual will converse without difficulty. Voice quality can also be subjectively monitored at this time. Persistent or progressive dysphonia may suggest an organic lesion in the larynx compared to intermittent dysphonia that may suggest a functional disorder.

It is not routine practice in the otolaryngology clinic to undress a patient in order to examine the respiratory system, but this should be done if the clinical history suggests chest disease, such as suspected metastasis or severe chronic obstructive airway disease (COAD) limiting fitness for surgery, that might influence the decision-making for the ENT condition.

Clinical signs and symptoms of upper respiratory impairment include:

- dyspnoea
- tachyponea
- stridor
- dysphonia
- cyanosis
- use of accessory muscles of respiration.

The examiner should be aware of general systemic signs of disease that are relevant to the respiratory tract, such as nicotine staining to the hands, clubbing, anaemia, jaundice and spider naevi.

Nasal airway

The upper airway begins with the nasal cavity and therefore the nasal airway should always be assessed. Although it is covered in Chapter 88, Outpatient assessment, a summary is provided here. Nasal airflow and patency should be subjectively assessed through each of the nares using the palmar surface of the thumb or a shiny Lack tongue depressor. Anterior rhinoscopy should be supplemented with endoscopic examination of the nose in order to inspect the posterior nasal cavity.

Laryngoscopy

Indirect laryngoscopy examination with a mirror, a technique with an illustrious history,[1] is still used as a method of visualizing the larynx. This examination method has several limitations including perceptual errors,[2] difficulties in the user reliably recording the side of lesion, the learning curve in acquiring and maintaining the skillset,[3] and a significant failure rate which, prior to the era

of readily available flexible endoscopy, often mandated direct endoscopy under general anaesthesia.

Significant advantages include widespread availability in all ENT departments, low cost to buy and maintain and a learning curve that is not insurmountable. Regular practice on all suitable patients in the early years (an anatomical model to facilitate this process has been described)[3] and continued later use can often maintain the skillset for this technique. A few studies exist on minor laryngeal procedures that can be carried out with indirect techniques successfully,[4–6] including obtaining photographic images as the sole operator. It is a procedure free of complications except for gagging and failure to visualize the lesion,[7, 8] which occurs more frequently than with flexible or direct laryngoscopy. Failure of indirect laryngoscopy suggests that microlaryngoscopy may be difficult.[9] Magnifying laryngeal and nasopharyngeal mirrors have been described.[10]

Endoscopic assessment, either with a rigid or flexible laryngoscope, has supplanted mirrors due to better optical resolution and higher sensitivity.[11, 12] Endoscopes in the ENT clinic should now be considered the standard of care.

The rigid Hopkins rod system uses 70- or 90-degree angled lenses and allows an excellent view of the larynx through a transoral approach. This is the favoured technique for laryngologists in the 'voice clinic' as the wider rigid rod lens produces a much higher optical resolution for more detailed assessment of phonation.[13] Laryngoscopy can be supplemented with stroboscopy, laryngography or digital acoustic voice analysis (see Chapter 62, Evaluation of the voice).

TECHNIQUE FOR FLEXIBLE LARYNGOSCOPY

The endoscope is passed through the anterior nares, along the floor of the nose under the inferior turbinate. Passage between the middle and inferior turbinate or through the opposite nostril may be necessary if the airway is narrowed. Once the endoscope is in the postnasal space, the patient is asked to inspire through the nose, and this opens the postnasal sphincter allowing passage of the endoscope into the oropharynx (**Figure 61.1**).

A stepwise assessment of the larynx is made: the vallecula is inspected (by tongue protrusion), the supraglottic larynx, followed by the glottic larynx. Attention should be taken to record accurately the correct side of any lesion identified as errors are common.[14] Newer extended applications of this technique include flexible endoscopic evaluation of swallowing, with or without sensory testing,[15] videoendoscopy of the hypopharynx and cervical oesophagus,[16, 17] including biopsy and foreign body removal through a biopsy channel, paediatric adenoid assessment[18] and neonatal upper airway assessment.[19]

Topical anaesthesia

Topical nasal administration of local anaesthetic is often used prior to flexible laryngoscopy in the clinic

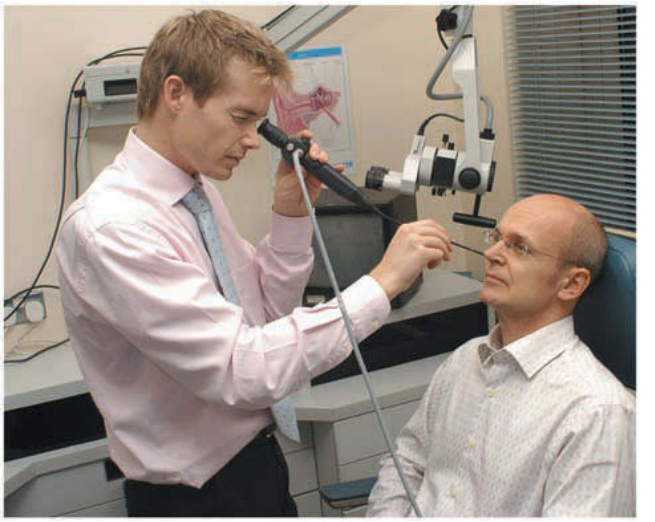

Figure 61.1 Flexible laryngoscopy in the clinic.

in order to decongest the nose and facilitate examination.[20] Cocaine was traditionally used in the past either as aerosol (10%) or as paste (4%). However, concerns regarding cardiotoxicity and drug misuse, as well as contamination from the delivery system for cocaine, have resulted in newer derivatives such as cophenylcaine or amethocaine being used.[21] Some authors have questioned the necessity of using any anaesthetic for this procedure.[22, 23] Eight randomized studies[21–28] have been published, of which four are double-blind randomized trials,[23, 24, 26, 28] but all have some methodological flaws. Unfortunately, two of the double-blind studies[24, 26] draw inappropriate conclusions from their data. A more recent systematic review of the few randomized control trials on this subject found no reduction in pain scores with the use of vasoconstrictive, topical anaesthetic or lubricating agents.[29] Further well-designed, sufficiently powered, double-blind studies incorporating all options are warranted. Overall, current evidence suggests that the benefits of local anaesthesia cannot be large in these circumstances.

Consent and complications

Informed consent prior to any surgical procedure is a fundamental aspect of clinical practice, to prevent patient-doctor complaints and medical malpractice claims. It has been suggested that all interventions, including laryngoscopy, require a consent form to be completed. Thus far, it is not routine clinical practice to obtain written consent before performing flexible laryngoscopy in the clinic. Currently, there is no literature on this subject.

No robust literature on complications of flexible nasoendoscopy exists, but these include discomfort of variable degree and occasional epistaxis during difficult insertion, excessive gagging in the absence of local anaesthesia, coughing, transient laryngospasm, gluteraldehyde allergy and infection due to laryngoscope contamination. Paediatric, including neonatal, flexible awake nasoendoscopy are now accepted procedures,

but, particularly in the latter group, the procedure may be associated with episodes of significant oxygen desaturation, laryngospasm, bronchospasm and coughing.[30] Some patients may experience psychogenic pain and other symptoms which may last for prolonged periods. The increased prevalence of MRSA, hepatitis B and C and HIV has resulted in more rigorous infection control systems to be implemented for all invasive procedures.

Decontamination principles

Sterilization practices used to vary considerably throughout the UK.[31] Most large hospitals have opted for a central decontamination unit to handle the sterilization of endoscopes in order to maintain optimum anti-infective standards, while some units use a chemical soak system, but the type of disinfectant, method of delivery and duration of soak used vary widely. A few hospitals use disposable sheath systems and some still only wipe endoscopes with alcohol wipes between patients. Protocols for high-risk patients demonstrated a parallel lack of uniformity. A similar divergence in practice has been recorded in South Africa[32] and other parts of the world.[33]

UK national guidelines for the cleaning of nasoendoscopes have now been produced.[34, 35, 36] The main points to come out of these guidelines are summarized below.[34, 37] The risk of transmitting infection between scope and patient has not been quantified for nasoendoscopes, but for gastroscopes it is 1 in 1.8 million. The risk of variant Creutzfeldt–Jacob disease transmission is probably extremely low provided scrupulous attention is paid to the detail of decontamination. The risk of transferring infection from the user to the scope is minimized by removal of all jewellery, including wristwatches, proper hand decontamination and the wearing of disposable gloves. Should an outbreak of infection occur, a logbook should be available which records patient details, time and date of use, name of user and person responsible for sterilization, and the method of sterilization. Details of the instrument used, including serial numbers, should be recorded in the patient's notes. Appropriate training programmes for all involved staff and an up-to-date list of authorized personnel and what each individual authorization covers should be available in each department. Policies need to cover these issues when the scopes are used in a variety of settings outside ENT departments. Even if a disposable sheath is the preferred mode of ensuring clean nasoendoscopy, daily high-level disinfection of the endoscopes is required.

Used endoscopes from locations distant to the site of decontamination should be transported to the place of decontamination in a labelled disposable bag in its case if possible. Decontamination involves both cleaning and high-level disinfection. Methods chosen need to be approved by manufacturers to uphold service contracts and warranties. Inspections of scopes should be visual and by formal leak testing.

Cleaning may be manual or mechanical but must remove all visible debris. It is no longer recommended to use gluteraldehyde for chemical high-level disinfection owing to its toxicity[38–40] and ability to fix proteins onto the endoscope surfaces, making their subsequent removal more difficult.[35] Suitable options for chemical disinfection include electrolyzed saline (Sterilox®); chlorine dioxide (Tristel®); peracetic acid (Steris®, Nucidex®, Perasafe®, Gigasept®). Peracetic acid is irritant to skin and the respiratory system.[34] Tristel is used by many ENT clinics in the UK.[34, 41]

There is no ideal disinfectant, with the choice of agent dependent on its microbicidal activity, toxicity profile and approval for use by the various endoscope manufacturers. Disposable sheaths are a safe and effective alternative to chemical decontamination and have been introduced in order to reduce the necessity of formal sterilization between examinations. These have been shown to be effective in acting as a barrier to infection, even by viral particles.[42] Sheaths currently available have an improved design that requires no special equipment for application and removal, which, if improperly used in the past, caused damage to the endoscope covering at the tips, making it costly or impossible to repair.[43] There is a risk of endoscopic contamination if the sheath is breached. No significant difference has been noted between sheathed and unsheathed endoscopes from the user and patient perspective, as well as in image quality.[44] This may well provide a much more cost-effective, user-friendly and safe solution to some forms of chemical disinfection.

Local or central automatic endoscope washer-disinfectors (AEWDs) are also gaining widespread use as they free up clinic support staff from the manual tasks involved in decontaminating endoscopes, as well as providing a standardized endoscope sterilization protocol which is very useful from a clinical governance perspective. The high set-up costs involved in acquiring AEWDs as well as the logistical challenge from the slow turnaround of endoscopes, especially if the central facility is at a distant site from the ENT clinic, are some of the disadvantages in opting for an AEWD system. Out-of-hours cleaning and disinfection of nasoendoscopes by junior medical staff is still a real problem, mainly due to lack of knowledge and access to the appropriate facilities, usually based in outpatient departments.[45]

Most ENT departments are implementing a flag system to record details of each laryngoscopy episode. Flexible endoscopes are expensive and relatively fragile instruments. They require careful handling, maintenance and cleaning; a designated health practitioner should be responsible for their care. Storage of endoscopes is best achieved with the scopes hung vertically in storage cupboards, or in custom-made storage/transport trays. This prevents repeated twisting and bending of the scope, which will result in breaking of the optical fibres, thus reducing the lifetime of the scope.

Considerations of consent, accurate documentation of findings and sterilization are important as they all have time and resource implications in the clinic.

KEY POINTS

- Indirect laryngoscopy is a technique with definite limitations, but its low cost, widespread availability and lack of associated complications should mean that it survives as part of the otolaryngologic skillset.
- Flexible endoscopy has rightly replaced the above as the first-choice tool for examination of the upper aerodigestive tract owing to its extended applications.
- The evidence for topical anaesthetic use, choice of agent and the extent of benefit is not clear-cut.
- There is no significant literature on consent issues.
- There is still debate as to the most cost-effective means of decontaminating flexible laryngoscopes. It is acceptable, however, to decontaminate endoscopes manually without a biopsy channel using chemical wipes such as chlorine dioxide, avoiding the high costs and logistical issues from the use of a central sterile services unit.[34,35]
- Gluteraldehyde is no longer recommended for use in the UK due to the high risk of sensitivity. Disposable sheaths are another alternative to minimize cross-contamination.
- Regardless of the decontamination protocol used, an adequate endoscope traceability system needs to be in place for clinical governance and risk-management purposes.

OPERATIVE LARYNGOSCOPY

Anaesthetic considerations for laryngoscopy in the operating theatre

Accurate assessment of the larynx under general anaesthetic requires a systematic approach involving cooperative work on the shared airway between the otolaryngologist and the anaesthetist. It is therefore important to develop a good working relationship with one's anaesthetic colleague and have a system that you are both happy to work with. When applied to appropriate patients, laryngoscopy, can be performed safely as a day-case procedure.[46]

There are several methods of performing laryngoscopy under general anaesthesia and there is a balance between maintaining a secure airway and obtaining a clear, unobstructed view of the larynx. A systematic review of each technique will be discussed, and the clinician must decide upon a technique that they find most satisfactory.

MICROLARYNGOSCOPY TUBE

The microlaryngoscopy tube is a small-diameter cuffed endotracheal tube (ET), which is placed in the posterior glottis. The diameter ranges from 16 to 22 French gauge. This type of tube has been shown to be safe for operative laryngeal microsurgery.[47] If transoral laser microsurgery is planned, specifically designed non-combustible non-reflective laser tubes are used. These have indicator dyes incorporated into the cuff to identify whether the cuff is damaged, in order to reduce the risk of an airway fire hazard.[48–50]

TOTAL INTRAVENOUS TUBELESS ANAESTHESIA

This technique involves anaesthesia maintained by continuous intravenous infusion of propofol with topical lignocaine and the patient breathing spontaneously. It has been described for both diagnostic and therapeutic laryngoscopy, including laser microsurgery. It is not recommended for high-risk patients (ASA III or IV) or patients with an obstructed airway. Total intravenous tubeless anaesthesia should only be undertaken by those who have expertise in this technique.[51–53]

HIGH-FREQUENCY JET VENTILATION

High-pressure jet (Venturi) ventilation of anaesthetic gases without an ET tube can be administered via the supraglottis, glottis or subglottis, or via the transtracheal/ cricothyroidotomy route. This technique has been widely used for endolaryngeal surgery, including laser surgery;[54] advantages include the absence of combustible material in the airway, thus providing a clear view of the larynx and deep anaesthesia to allow for microsurgery.[53] Large multicentre studies of 643 patients based in France and 872 patients in the USA have shown low complication rates using this technique. Problems such as pneumothorax were encountered in 1%, hypoventilation in 2% and surgical emphysema in 8% of cases.[55,56] The Venturi technique has also been described in paediatric practice.[57] Relative contraindications to using this technique would be the unstable or obstructed airway, difficult access to the larynx (micrognathia/overhanging teeth) or respiratory failure (with emphysematous bullae).[57,58]

RIGID LARYNGOSCOPY

The patient is prepared and anaesthetized as standard for the operating theatre. The position is supine, with head extension and neck flexed in order to open the laryngeal inlet. Eye cover, dental protection and antiseptic draping are applied.

The widest laryngoscope to maximize vision is passed perorally in the midline and the tongue is negotiated in order to visualize the epiglottis. Care must be taken to prevent dental trauma and trauma to the lips. The endoscope is used to elevate the epiglottis in order to visualize the larynx. Different telescopes can be utilized to inspect the subsites of the endolarynx (**Figure 61.2**), such as the anterior commissure scope, which is designed to

Figure 61.2 A selection of rigid endoscopes for laryngoscopy.

maximize the view of the anterior glottis. Suspension of the laryngoscope frees both hands to operate.

Rigid laryngoscopy offers improved visualization of the larynx through better illumination, higher magnification and wider and deeper fields of vision. By incorporating the microscope and combination of 0, 30 and 70 degree angled endoscopes, a full view of the endolarynx can be obtained (**Figure 61.3**). The angled endoscopes allow better perspectives of the ventricle, free edge and under surface of the vocal cord. It is important to define and record accurately the findings of the laryngoscopy. The site, extent, dimensions, shape, colour and surface characteristics of the lesion should be defined. Vocal cord mobility and airway patency should be recorded. The use of printed operative diagrams should be encouraged (**Figure 61.4**).

Photo documentation is becoming an important part of otolaryngology practice. It improves case review between clinicians and is increasingly forming part of routine practice in the current medicolegal climate. High-resolution digital imaging is now available to facilitate still, video and hard-copy documentation.

NEW TECHNIQUES IN LARYNGEAL ENDOSCOPY

Optical imaging techniques have evolved over the past two decades from our greater understanding of fluorophores, the fluorescent properties of intracellular and extracellular components, as well as advancing laser, optical filters, endoscope and computer software technology. As always, the challenge with new technology is defining how it can be incorporated into daily clinical practice, given the variation in requirements during assessment of the upper respiratory tract and the group of patients or clinical scenario: for example, general population versus those at high risk of neoplasia, determining precancerous versus malignant lesions, assessing tumour margins intraoperatively, or post-treatment surveillance following primary surgical treatment versus chemoradiation therapy. The gold standard against which these new technologies are compared is histopathological analysis and, while the sensitivity, specificity and accuracy of the techniques described below are still under investigation, none yet matches the gold standard.

Figure 61.3 Theatre set-up for rigid laryngoscopy under general anesthesia. Note the telescope and the two-handed technique to assess, document and obtain biopsy.

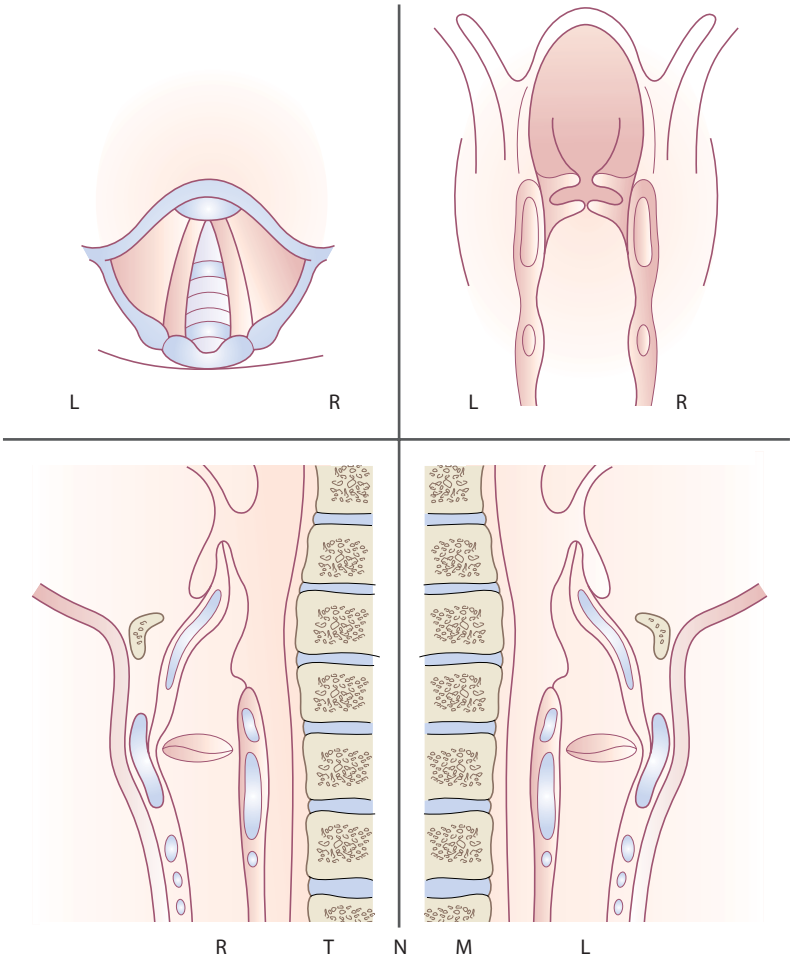

Figure 61.4 Printed operative diagrams used to record findings.

Contact endoscopy and microlaryngoscopy

This new technique allows for microscopic assessment of the epithelial cells of the larynx *in vivo* and *in situ*. The process involves staining the epithelium with methylene blue or Lugol's iodine. A modified Hopkins rod laryngoscope is applied against the mucosa of the larynx. At ×60 and ×150 magnification cytological characteristics of the cells, nuclei and cytoplasm can be appreciated in the first three layers of epithelial cells, in addition to the subepithelial microvascular network.[59] Premalignant conditions, such as dysplasia, could therefore potentially be detected earlier. It is designed not as a substitute for histology but as a research tool to allow better understanding of the cytological changes that occur in the laryngeal epithelium in the transition from normal to disease. Preliminary studies have shown good correlation between its findings and formal histology,[60,61] with sensitivity and specificity of 90% and 94% respectively, and an 88% agreement with histopathological findings after appropriate training.[62] The use of contact endoscopy in the larynx is confined to clinical research but does show promise for a wider application in the future.

The main advantage is that it is a non-invasive procedure, and avoids complications related to unnecessary tissue biopsy, especially in irradiated patients. The technique, however, is limited by the superficial depth of penetration, the inability to distinguish confidently between intraepithelial neoplasia and invasive carcinoma, the experience required to minimize trauma to delicate tissues with the endoscopes, and the impaired visualization of malignant cells in the presence of scarring, chronic inflammation or keratosis.

Autofluorescence

Various extracellular and intracellular structures such as collagen, elastin, mitochondria and porphyrins naturally emit light following absorption of light at a specific wavelength. This physical phenomenon is a property of fluorophores. Knowledge of the specific wavelength at which specific fluorophores are excited allows investigators to take advantage of particular intracellular or extracellular constituents that may be altered in the disease state and consequently stimulated using monochromatic light in the blue or ultraviolet range of the electromagnetic spectrum (wavelengths between 375 nm and 460 nm), in the form of a laser. Normal mucosa fluoresces green, while neoplastic mucosa has reduced autofluorescence and emits a red-violet colour (**Figure 61.5**).[63,64] Changes in autofluorescence can be detected by sophisticated endoscopes or observed as spectral changes using optical filters and specialized detectors.

When combined with microlaryngoscopy, autofluorescence may be better at identifying invasive carcinoma, with a reported sensitivity of 87–97% and specificity of 78–87%.[65–69] The limitations of autofluorescence are the difficulty in assessing the basal mucosal layer due to a restricted depth of penetration, and the low specificity, with false positives arising from granulation tissue, scarring and chronic inflammation. Further studies are required to determine the benefits of microlaryngoscopy and autofluorescence in increasing detection of discrete upper airway lesions, and in reducing the rate of positive margins following surgery, but there is a paucity of work using this tool, indicating that it may be on the wane.

Narrow-band imaging

White-light laryngoscopy is limited by the inability to detect very small epithelial changes and is also unable to differentiate between benign and malignant lesions *in vivo*. Narrow-band imaging (NBI) is a novel endoscopic technique which aims to overcome some of the limitations of white-light endoscopy by using filtered light to visualize mucosal and submucosal neoangiogenic microvascular patterns that have been characterized previously.[70, 71] Certain neoangiogenic features such as intraepithelial papillary capillary loops are associated with precancerous and malignant mucosal lesions (**Figures 61.6** and **61.7**).

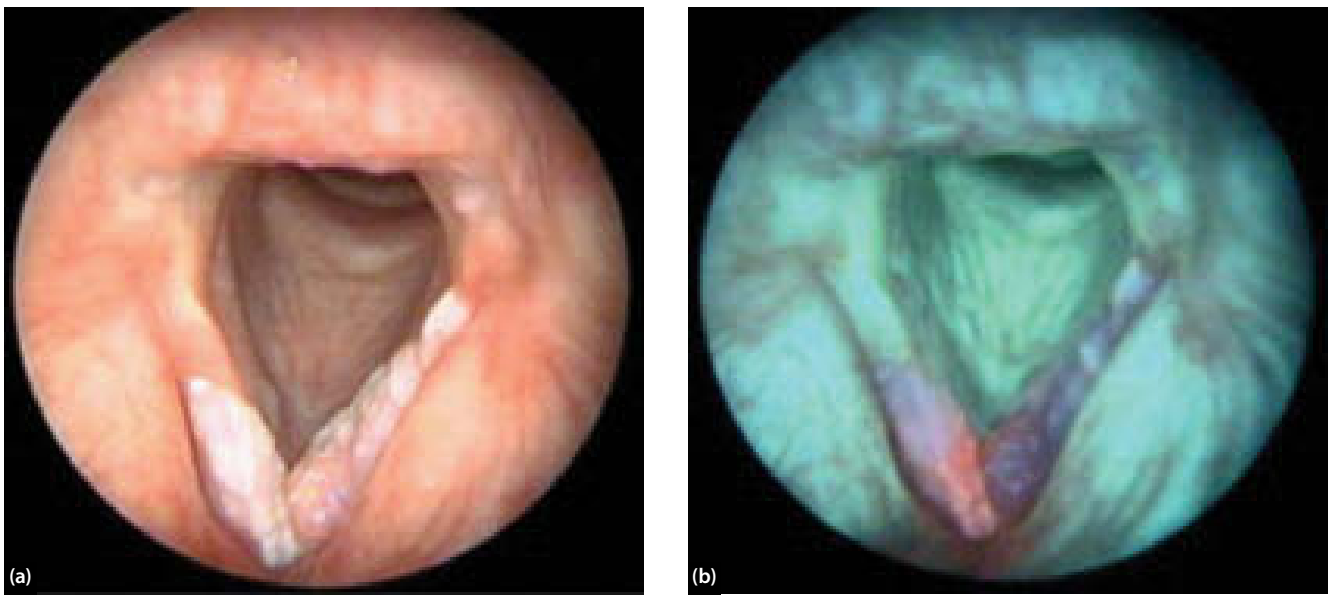

Figure 61.5 **(a)** White-light image shows an abnormal lesion on the right cord, suggestive of a neoplastic process. **(b)** Autofluorescence endoscopy shows loss of autofluorescence, giving an orange/red colour, typical for invasive malignancy. With Permission fom Springer Nature, from Arens C, Dreyr H, Glanz et al. Indirect audofluorescence laryngoscopy in the diagnosis of laryngeal cancer and its precursor lesions. *Euro Arch Otorhinolaryngol* 2004.

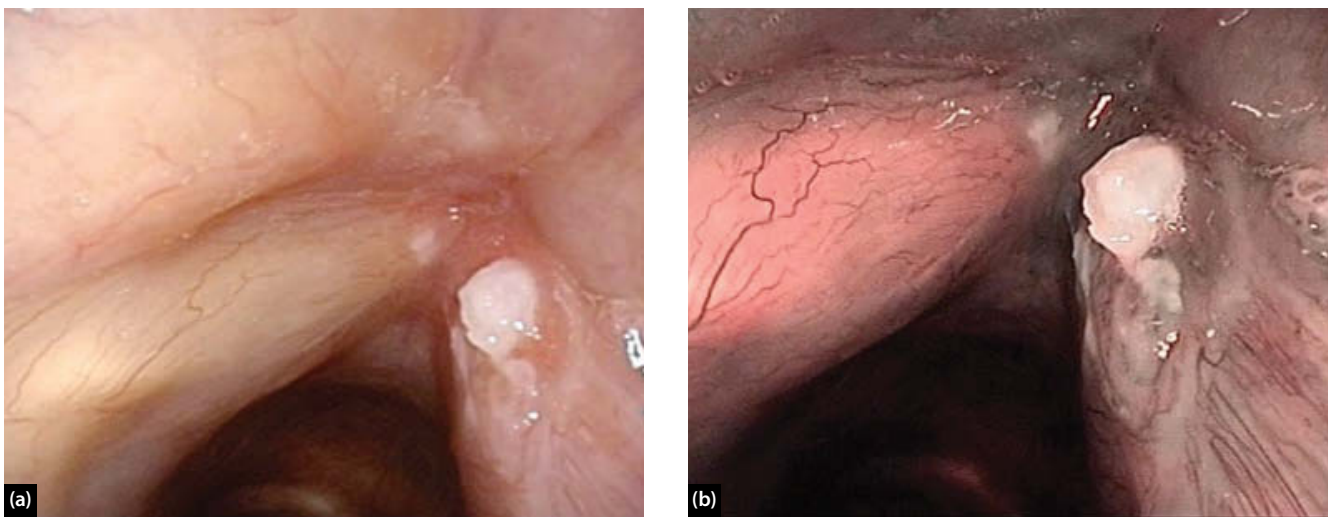

Figure 61.6 **(a)** White-light image shows an area of leukoplakia on the right glottis. **(b)** Narrow-band image shows a carcinoma *in situ*, with better definition of margins (inferior extension and satellite lesion extending in the ventricle). (Image courtesy of Professor Cesare Piazza, University of Brescia.)

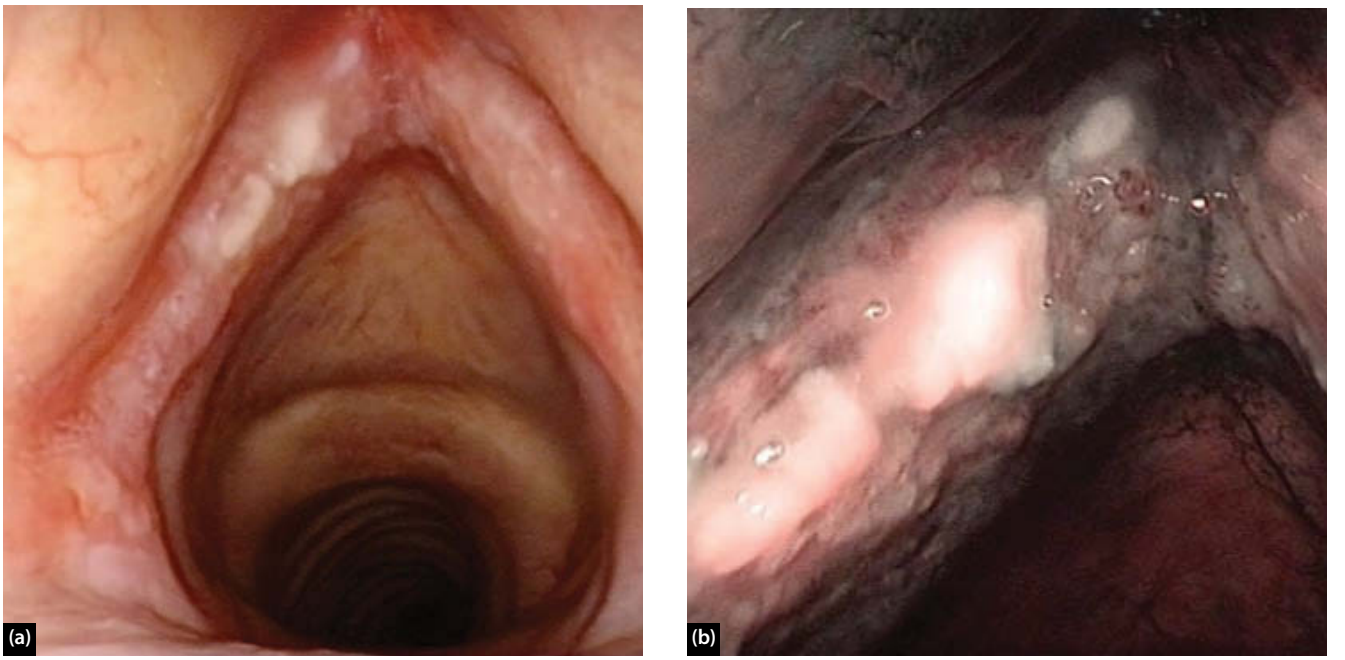

Figure 61.7 **(a)** White-light image shows an abnormal glottic lesion. **(b)** Narrow-band image shows findings typical of squamous cell cancer and also reveals extension to the contralateral cord. (Image courtesy of Professor Cesare Piazza, University of Brescia.)

NBI technology is based on knowledge that the depth of light penetration is a factor of its wavelength, and through the use of special filters, blue and green light are selected from white light, corresponding to the peak of absorption of haemoglobin. Narrow-band blue light (415 nm) highlights superficial capillary networks, while narrow-band green light (540 nm) displays subepithelial vessels and, in combination, the two wavelengths produce a very high-contrast image of the tissue surface, which is particularly evident when using a high-definition television (HDTV) camera.

NBI has been able to achieve sensitivity and specificity of 89% and 93% respectively in the diagnosis of primary laryngeal lesions,[70] and higher values have been achieved in the context of assessing lesions following radiation and chemoradiation therapy,[72] therefore reducing the requirement for a tissue biopsy in these cases.

NBI mode is a standard feature on some videoendoscopes, thus making the technique readily available. However, it is limited by the learning curve required to understand aberrant microvascular architecture and, as with other optical imaging techniques, the superficial depth of penetration precludes assessment of the deep extent of neoplasia.

Optical coherence tomography

Optical coherence tomography (OCT) is an analogue of ultrasound, using light instead of sound to produce a high (micrometre) resolution cross-sectional image, similar to a vertical histological section (**Figure 61.8**).[73] A beam of light is directed onto tissue and back-reflected from components with different optical properties. Because the velocity of propagated light is several magnitudes greater than sound, and the resultant echo time delay cannot be measured using conventional electronics, a specialized technique known as interferometry is required to measure echo time delay and the intensity of back-reflected light. Interferometry uses light that has travelled a known reference path length and time delay.[73]

A number of investigators have used endoscopic versions of OCT to analyze both healthy and diseased laryngeal mucosa. In combination with microlaryngoscopy, OCT has been shown to significantly increase the sensitivity of determining benign versus malignant lesions and the grade of precancerous lesions when compared to microlaryngoscopy alone.[74] Further studies are needed, however, to determine whether the optical biopsy derived from OCT can indeed replace an excisional tissue biopsy.

Fluorescence lifetime imaging

Fluorescence lifetime imaging (FLIM) is another non-contact optical method which has several advantages over contact endoscopy, providing complementary ultrastructural and spectral detail. FLIM is based on the principle that the fluorescence lifetime of a fluorophore depends on its molecular environment but not on its concentration. Molecular effects in a sample can therefore be investigated independently of the variable and usually unknown concentration of the fluorophore (**Figure 61.9**).

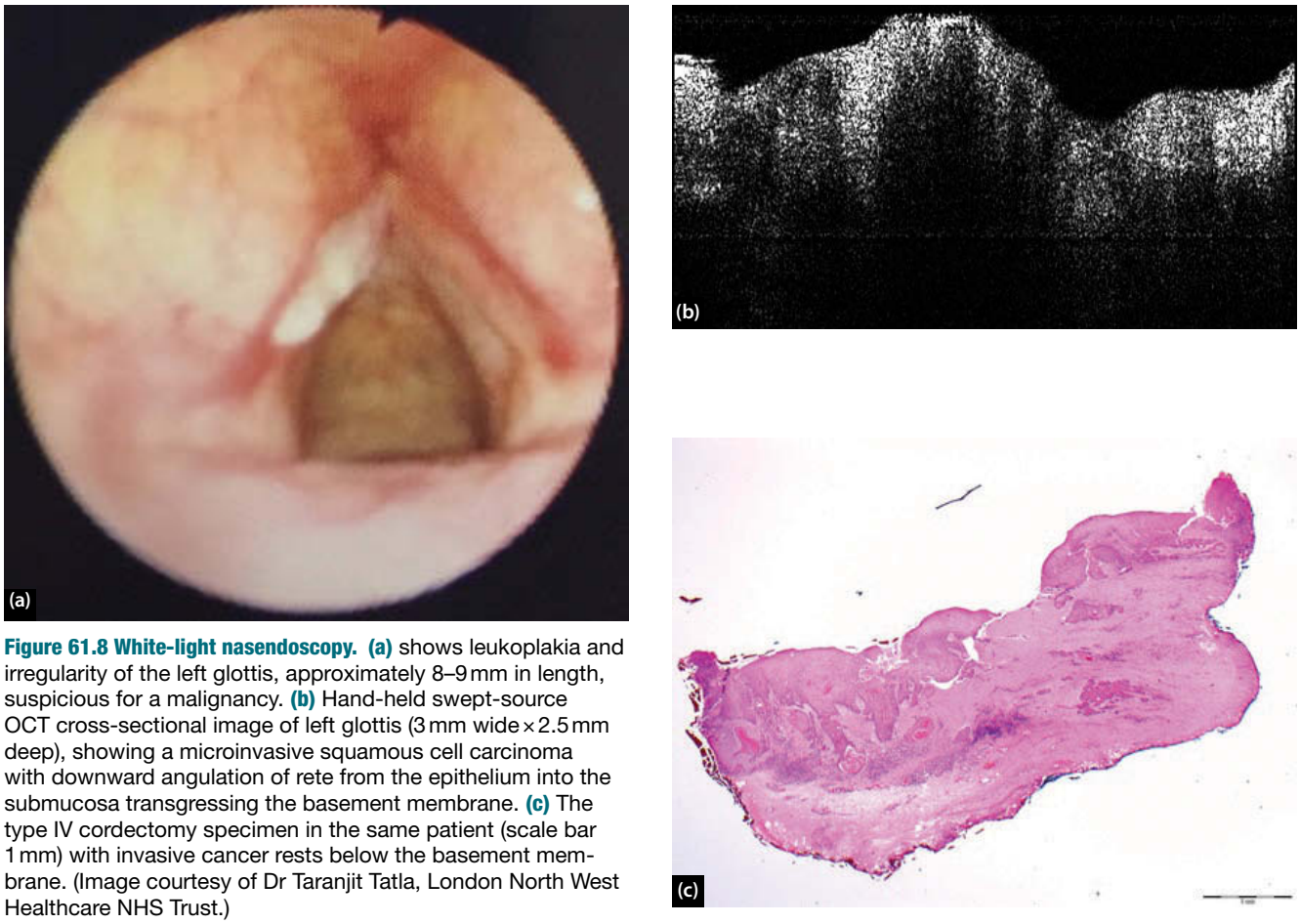

Figure 61.8 White-light nasendoscopy. (a) shows leukoplakia and irregularity of the left glottis, approximately 8–9 mm in length, suspicious for a malignancy. **(b)** Hand-held swept-source OCT cross-sectional image of left glottis (3 mm wide × 2.5 mm deep), showing a microinvasive squamous cell carcinoma with downward angulation of rete from the epithelium into the submucosa transgressing the basement membrane. **(c)** The type IV cordectomy specimen in the same patient (scale bar 1 mm) with invasive cancer rests below the basement membrane. (Image courtesy of Dr Taranjit Tatla, London North West Healthcare NHS Trust.)

Laryngeal ultrasonography

Ultrasound scanning is a well-established method of imaging in the head and neck. A new application of this technique in the larynx involves applying the ultrasound probe against the external surface of the larynx during microlaryngoscopy. This holds potential in providing information regarding invasion of deeper compartments of the larynx, such as paraglottic and pre-epiglottic spaces.[75] The usefulness of this technique in laryngology is still being evaluated.[76, 77]

Assessment and management of the obstructed or difficult airway

Those patients who present for endoscopic assessment with upper airway obstruction pose a complex problem for the otolaryngologist and anaesthetist. This short section will discuss the assessment of these patients and provide a management algorithm. A further discussion on detailed management of the obstructed airway can be seen in Chapter 72, Upper airway obstruction and tracheostomy.

PRE-OPERATIVE ASSESSMENT

Pre-operative assessment must be carried out in order that both surgeon and anaesthetist are prewarned of potential problems. Mild to moderate chronic airway obstruction may exist undetected, as these patients may have compensated over time compared to individuals who present with acute severe airway dysfunction. The presence or absence of stridor at rest or on exertion, lying flat, or when bending down, decreased exercise tolerance and nocturnal dyspnoea when lying supine are all indicative of a problem. An assessment of the patient's respiratory reserve is essential. Those patients with respiratory failure will tend to desaturate rapidly if there is prolonged or difficult intubation. A difficult airway can be anticipated in medical conditions such as rheumatoid arthritis, obstructive sleep apnoea, acromegaly and mucopolysaccharidosis, and in craniofacial syndromes, particularly Treacher Collins and Pierre Robin syndromes. Specific features include short neck, receding jaw, maximal mouth opening less than three fingerbreadths, inability of the lower jaw to protrude beyond the upper jaw (jaw slide) and a short thyromental distance less than three fingerbreadths indicating high larynx. The Mallampati score, which classifies visibility of oropharyngeal structures, is used to predict the ease of endotracheal intubation. The anaesthetist usually carefully assesses these specific features, but some appreciation of the potential problems by the surgeon is important. Prediction of potential airway difficulty is a complex business but can be rewarding when severe or obvious problems are identified. When there are no obvious problems, evaluation is imperfect and safe airway management depends on the adoption of a strategy that is able to respond to unexpected difficulty with intubation or oxygenation.

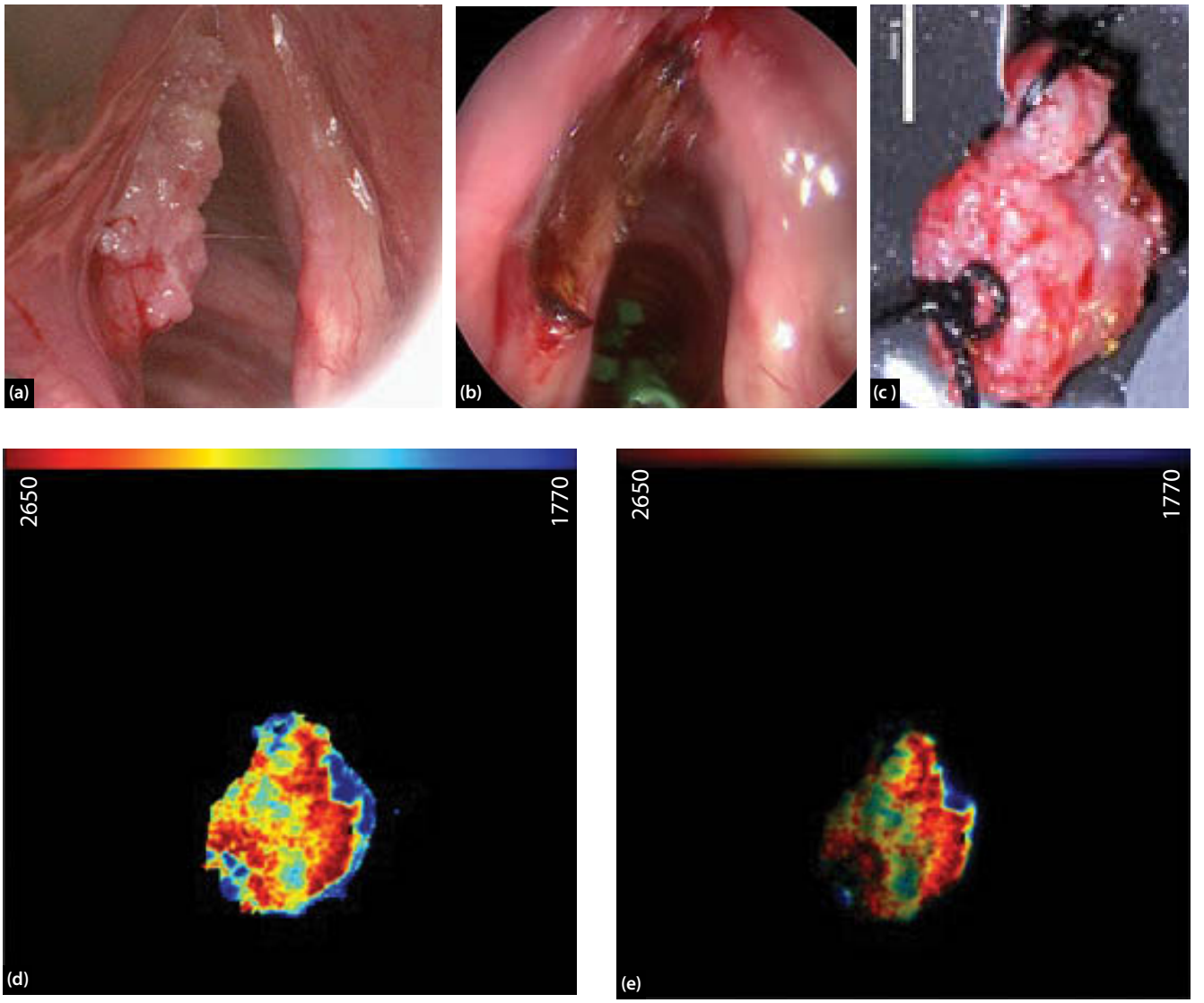

Figure 61.9 **(a)** White-light 00 rigid Hopkins rod endoscope view (high-definition TV) of glottis lesion with irregular surface outline, staged T1a. Previous biopsy has confirmed this to be a moderately differentiated squamous cell cancer in the left glottis in a background of carcinoma *in situ*. **(b)** CO_2 transoral microsurgical laser excision of left glottis lesion (type IV cordectomy). **(c)** Anteroposterior, medial-lateral orientation of resected glottis specimen with suture markers for pathology sectioning and reporting. **(d)** The fluorescence lifetime image map and **(e)** the specimen intensity-merged fluorescence lifetime image map. Reduced fluorescence lifetime (green) appears to correlate with the pathologist-reported extent of carcinoma *in situ* (cis extending to the lateral margin of the specimen). There appear to be islands of reduced lifetime amid islands of longer lifetime (yellow/orange/red) which would not be atypical for mucosal carcinoma *in situ* changes. Histopathology reported a 1 mm cancer, lying 1 mm from the lateral margin, 3 mm from the medial margin and 1.5 mm clear of the resected deep margin. (Image courtesy of Dr Taranjit Tatla, London North West Healthcare NHS Trust.)

Specific investigations other than careful flexible nasoendoscopy are rarely safe in acute airways obstruction but plain radiographs, CT/MRI and flow loops may well be indicated in chronic stable obstruction, particularly in suspected subglottic lesions. All patients undergoing panendoscopy for stridor should be counselled and consented regarding the possibility of a tracheostomy being performed.

OPERATIVE MANAGEMENT

Securing a safe airway is the primary aim of the procedure, followed by an accurate assessment of the cause, level and degree of airway obstruction and a biopsy if necessary. It should be remembered that tumours of the supraglottic larynx and tongue base are a particular problem. A moderate chronic airway obstruction may develop into complete obstruction with respiratory arrest when the patient lies supine with muscle relaxant administered. Tumours may be haemorrhagic and friable and this may make the intubation difficult.

The difficult intubation equipment should be ready for these patients, which includes a selection of rigid laryngoscopes and bronchoscopes, intubating bougies/guidewires, ETs and fibre-optic intubation equipment. The team should decide upon the following options for airway management:

- awake fibre-optic intubation
- induction anaesthesia and endotracheal intubation with/without guide wires or bougies, or by the surgeon using rigid endoscopes

- induction anaesthesia and jet ventilation (endolaryngeal or percutaneous)
- local anaesthetic tracheostomy.

The chosen airway strategy must have a plan A and plan B, for intubation, ventilation and extubation (see Chapter 72, Upper airway obstruction and tracheostomy).

The patient is asked to breathe 100% O_2. Looking at the bag will indicate the degree of airflow. Anaesthesia may be induced in the operating theatre; alternatively, the surgeon should be in the anaesthetic room with the rigid laryngoscope ready and tracheostomy set available for a surgical airway to be secured if necessary.

Failed intubation

If the anaesthetist is unable to identify the glottis and intubate, the patient should be maintained with the facemask and reoxygenated. The ENT surgeon should then attempt endotracheal intubation. The rigid bronchoscope is often quoted as a useful method of finding the glottis in difficult airway patients. The authors' preference is to use the anterior commissure endoscope to visualize the glottis. A rigid bougie can be passed through the scope into the trachea and a small ET tube passed over it.

In certain difficult cases with the airway obstructed by tumour, a retrograde intubation approach can be adopted. The rigid laryngoscope scope can be passed into the hypopharynx and then slowly withdrawn, with the tip angled anteriorly to see the glottis.[78, 79]

Tracheostomy under local anaesthetic is not an easy procedure in a patient with an acute airway obstruction. Consent for emergency tracheostomy should always be taken when planning any surgical procedure that may have an associated significant risk of airway obstruction. The patient is positioned in the supine position with sufficient neck extension to allow palpation of the trachea. In the conscious patient, constant reassurance is mandatory as the patient may be struggling and unable to lie still for a long period of time. Pressure on the larynx during dissection may worsen the patient's sense of obstruction. Local anaesthesia (20 mL of 1% lignocaine) should be injected if time or patient condition permits and is strongly advocated.

The operation is more difficult in small children and adults with adipose necks because of the difficulty in tracheal palpation. A vertical midline incision is made from the inferior aspect of the thyroid cartilage to the suprasternal notch and continued through the infrahyoid muscles and thyroid isthmus irrespective of bleeding, although an experienced assistant providing suction and retraction is most helpful.

After carefully palpating for the cricoid cartilage in order to avoid cutting it, a vertical incision is made in the trachea from the second to fourth ring, the knife rotated through 90 degrees and an appropriate tube rapidly inserted. Thereafter, haemostasis is obtained, and all blood suctioned out of the airway. Once the situation is under control, it may be appropriate to refashion the tracheostoma to prevent later complications. After securing the airway, general anaesthesia is induced and endoscopy proceeds. A detailed discussion of the compromised airways can be found in Chapter 72, Upper airway obstruction and tracheostomy.

BEST CLINICAL PRACTICE

- ✓ Examination of the upper aerodigestive tract should include:
  - ✓ flexible nasolaryngoscopy
  - ✓ microlaryngoscopy
  - ✓ Hopkins rods and telescopes
  - ✓ photo documentation.
- ✓ Careful clinical history taking and traditional examination techniques still yield useful results, particularly when technology fails.
- ✓ Flexible endoscopy is a widely used simple technique whose role is being extended to cover swallowing assessment, cervical oesophagoscopy, biopsy and foreign body removal, as well as paediatric and neonatal assessment.
- ✓ Current evidence suggests that local anaesthesia prior to flexible nasolaryngoscopy confers no significant advantages, but cost issues around cophenylcaine use are significant.
- ✓ Infection control issues around flexible endoscopy still require clarification but the newer sheaths may provide an alternative to chemical disinfection systems and their attendant risks.

KEY POINTS

- Close cooperation with anaesthetic colleagues in deciding how the airway will be shared is essential.
- The correct patient position for rigid laryngoscopy is supine, with the head extended and neck flexed to open the laryngeal inlet.
- Modern rigid and microlaryngeal endoscopy equipment has greatly improved visualization and tissue handling, but the principles of use remain essentially unchanged.
- A wide choice of rigid laryngoscopes is available. Usually the widest scope to maximize vision should be chosen with suspension allowing both hands free for the surgeon. Accurate recording on preprinted diagrams and/or photo documentation is ideal and the latter will increasingly become the norm. Visualization of difficult areas can be improved with the use of specialist rigid scopes and/or angled Hopkins rods.
- New techniques to assess the upper respiratory tract include contact endoscopy, autofluorescence, narrow-band imaging, optical coherence tomography and laryngeal ultrasound.
- The management of the obstructed airway will always remain among otolaryngology's greatest challenges but has been hugely facilitated by the much wider availability of awake fibre-optic intubation skills in most anaesthetic departments.

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CHAPTER 62

EVALUATION OF THE VOICE

Julian A. McGlashan

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SEARCH STRATEGY

Data in this chapter may be updated by a Medline search using the keywords: voice quality, voice analysis, voice disorders, voice measurements, acoustic analysis, quality of life questionnaire.

GENERAL CONSIDERATIONS IN VOICE EVALUATION

Definitions

Speech is the expression of or the ability to express thoughts and feelings by articulate sounds.[1] The term **voice** is often used to refer to speech as a whole. However, when used in the context of voice evaluation, it is generally restricted to the acoustic output resulting from the interaction of vocal fold vibration with the vocal tract in vowel production.[2, 3] **Phonation** is a term used to describe the physical and physiological processes of vocal fold vibration in the production of speech sounds.[3] Impaired voice production due to abnormal vocal fold vibration is known as **dysphonia,** while no voice or whispery voice associated with no vocal fold vibration is termed **aphonia.**[4] **Hoarseness** is a non-specific, general term used to describe any change in voice quality.[5]

Normal speech and voice production

Normal voice production requires three essential elements:

- a pressure gradient across the vocal folds created by the flow of expired air from the lungs against the partly close vocal folds
- vocal folds of appropriate structure, mass and elasticity that approximate with appropriate tension to allow them to vibrate at a range of frequencies
- a resonating chamber, the vocal tract, whose size and shape can be changed to modulate the acoustic properties of sound generated by the vocal folds.

Speech consists of both these 'voiced' sounds, where the vocal folds vibrate, and 'unvoiced' sounds, where the is no vibration. Examples of 'voiced' sounds include English vowels (e.g. /a/, /e/, /i/, /o/, /u/) and some consonants (e.g. /b/, /d/, /g/, /v/, /n/, /l/, /w/, /j/). Consonants are produced by the sudden release of air from other parts of the vocal tract (e.g. lips for /b/) or aperiodic turbulent airflow (noise) through constrictions of the vocal tract (e.g. between the lips and teeth for /v/). Pure 'unvoiced' consonant sounds include /p/, /t/, /k/, /f/, /th/, /s/, /h/ where there is no associated vocal fold vibration. Together they provide the framework on which spoken language is constructed.[6] For more information see Chapter 60, Voice and speech production.

In voice evaluation the main focus of interest has been on the acoustic output resulting from the interaction between vocal fold vibration and modulating effect on the sound by the vocal tract in the production of vowels. To understand the relevance of some of these measures it is important to summarize the essential features of the acoustic properties of voice. Vocal fold vibration, acting as the sound source, produces a laryngeal tone which is a complex sound wave that, if heard without the vocal tract, has a buzzing quality. The sound wave can be characterized acoustically in terms of fundamental frequency (Hertz or Hz), frequency spectrum amplitude and intensity (dB).[3] The rate of vibration of the vocal folds (cycles per second) determines the fundamental frequency (F_0). Normal vocal fold vibration, however, does not simply produce a pure tone (sine wave) like, for example, a tuning fork. It consists of a spectrum of frequencies which are multiples of this fundamental frequency. They are called harmonics or overtones and are of varying amounts of energy or sound intensity.[3] Sound intensity decreases by approximately

12 dB for every doubling of the fundamental frequency (harmonic).[3] This relationship between the harmonics and sound intensity can be displayed in the form of a spectrum (see 'Normal voice' below). For breathy voices the energy decreases more rapidly at higher frequencies but is maintained in more strident voices which project more.

In addition, the vocal tract acts as a filter, selectively reducing the energy in specific bands of frequencies from the sound source (vocal folds) while allowing others to pass with maximum levels.[3] It acts in a similar fashion to pressing the keys on the bore of an oboe to alter the resonant properties of the instrument. The bands of frequencies that retain their energy levels reflect the resonant properties of the vocal tract and are known as formants. Altering the shape and dimensions of the vocal tract by changing the height of the larynx, position of the tongue, soft palate and lips changes the resonant properties of the vocal tract and formants. Correct production of formants is essential to allow distinction between different speech sounds.

For good and 'normal' voice production three conditions are required:

- quasi-periodic vibration of the vocal folds
- a well-defined harmonic structure of the voice signal radiating from the mouth
- a voice signal that is loud enough or has enough sound intensity (energy) to overcome the threshold of hearing of the listener.

Altering the height of the larynx, positioning of the tongue, soft palate and lips changes the dimensions of the supraglottis, pharynx and oral cavity. This in turn causes certain bands of harmonics to be preferentially reduced (damped) or enhanced. The effects on the perceived sound is to alter the formant structure or its quality (e.g. 'brassy', 'nasal').[7] For example, each vowel can have the same fundamental frequency but may be distinguished by the relative prominence of bands of harmonics (formants) and have an additional quality such as 'brassy' or 'breathy' by the relative prominence or absence of the energy at specific frequencies.[3, 6] Overall, there must also be enough energy (sound intensity) in the voice projected from the lips in order to excite adequate vibration in the listener's hearing mechanism. Increased loudness requires increased subglottal air pressure and abrupt and appropriate duration of closure of the vocal folds during the vibratory cycle to allow efficient conversion of aerodynamic energy into acoustic energy and vocal tract shaping particularly at higher frequencies.[3]

Pathological voice production

Abnormalities in the vocal folds, dimensions or structure of the vocal tract and inadequate control or amount of subglottic pressure can all contribute to a pathological voice. Abnormalities in the mass, elasticity and tensioning of the vocal folds can have two main effects: on the frequency rate and on the regularity of vibration. Alterations in frequency may lead to the voice being perceived as being too high or too low in pitch for the speaker's age and gender. It may also lead to restrictions in the dynamic frequency range of the voice during speaking or singing. Additional supraglottic structures such as the false folds, aryepiglottic folds and mucosa over the arytenoids can also be induced to vibrate either at the same time or in lieu of the vocal folds, providing an additional or alternative sound source. Irregular vibration of the vocal folds, caused by the abnormalities described above, will affect voice quality by producing a less clear fundamental frequency and harmonic structure. This irregularity is perceived as hoarseness and roughness.

Another important influence on the harmonic structure is the addition of noise to the voice 'signal'. For a listener, this may be environmental noise (e.g. trying to hear someone when there is loud background noise) or contained within the speaker's voice itself. For example, if there is a gap between the vocal folds during phonation, air will escape causing turbulent air flow which is perceived as noise (sound energy across all frequencies), reducing the relative amount of energy in the harmonic components and increasing the energy in the subharmonic components.[3] This is perceived as both hoarseness and breathiness or a voice lacking in power (asthenia). Alterations in the relative size, shape and length of the vocal tract, for example from a mass, increased pharyngeal muscle tension or reflective properties of the vocal tract, can all influence the energy levels and harmonic structure of the radiated sound causing the voice to sound strained or effortful.

Normal voice

Every human voice is unique because of anatomical, physiological, psychological, cultural, sociolinguistic and behavioural factors. In addition, a wide range of information about the speaker's gender, age, personality, emotional status and physical health is conveyed by their voice quality, pitch range and the systematic use of pitch patterning (intonation). Defining what is a normal voice is therefore difficult as there is a spectrum of what is considered normal. This can vary between different cultures and there is a continuum between 'normal' and 'dysphonic' sounding voices.[4] A generally accepted and pragmatic definition of a normal voice is one described as having the following characteristics:

- It is audible, clear or stable in a wide range of acoustic settings
- It is appropriate for the gender and age of the speaker
- It is capable of fulfilling its linguistic and paralinguistic functions
- It does not fatigue easily
- It is not associated with discomfort and pain on phonation.

Pathological voice

Pathological voice can be defined pragmatically as one that does not fulfil the criteria above. Variations in voice quality can provide valuable cues about our current emotions, physical health and psychological well-being. Patients generally

seek a consultation about their voice complaint because it causes one or more of the following problems:[8]

- **impairment**, i.e. an alteration in the structure or function of the vocal apparatus (structural abnormality, inflammation, neuromuscular abnormality or muscle tension imbalance) causing symptoms such as hoarseness, a weak voice, pitch change, throat discomfort
- **limitation in activity**, such as a reduction in vocal range in singing or the voice tiring or becoming hoarse with prolonged use in a noisy environment or if raised
- **participation restriction**, e.g. not being able to work or sing in a choir as a result of the voice problem.

The consequences of voice problems can therefore be one or more of the following: physical, functional, psychosocial, occupational and financial.

Potential use of voice evaluation

There are four main potential uses for voice evaluation:

- to provide a measure of severity of the disorder and degree of variance from established normal values
- as an outcome measure to help assess responsiveness to treatment
- to help during voice therapy to set therapy goals, in education about voice production and help patient achieve a target production[10]
- to help characterize the voice and voice problem, thereby providing supportive evidence for a differential diagnosis and pointers for treatment.

Overview of methods of objective evaluation of voice used in clinical practice

There are many hundreds of methods of assessment of the voice and voice production that have been developed over the years but the relevance of many of them to patients' complaints is often not clear. Visual assessment of the larynx (including, on occasions, diagnostic microlaryngoscopy) remains mandatory for confirmation of diagnosis in all cases and this is discussed further in Chapter 61, Assessment and examination of the larynx.

The most commonly used methods of evaluation in the UK are patient self-reported questionnaires and perceptual evaluation of the voice. It is argued that both are inexpensive, with the former giving a (subjective) measure of the impact of the 'pathological voice' on the patient's quality of life and the latter a semi-objective assessment of voice quality. They can be used to measure severity of the condition and as a therapeutic outcome measure.

To help with target production during therapy and characterize the voice or voice problem, and provide specific objective outcome measures, other more instrumental techniques are required. These include measures that relate directly to the voice signal (acoustic measures) or indirectly to the function of the vocal system, such as electrolaryngography (also called electroglottography), aerodynamic measures, voice accumulator measurements and combined measures (**Table 62.1**). No single measure can satisfactorily fulfil all functions and a multidimensional approach is ideally required. This, however, is a balance between the time, effort and expense it takes to perform versus its value in the management of the patient.

Previous high hopes that acoustic and other measures would provide a non-invasive means of diagnosing voice conditions have not been realized to date due to poor specificity and sensitivity. Attempts have been made to set standards for measurement and assessment.[10–12] These have largely been developed from expert consensus opinion and as a whole are not widely used in routine clinical practice in the UK.

SPECIFIC MEASURES

Quality-of-life measures

The need for treatment is largely determined by the patient's degree of disability, i.e. their perceived impairment, limitation in activity and participation restriction.[8, 13, 14] Various disease-specific patient questionnaires have been developed (**Table 62.2**) which allow self-reported grading of the effect of the voice problem on quality of life.[15–21] They have also been used as an outcome measure and indicator of response to treatment.[15, 22–24] Of these, the VoiSS questionnaire[18] has undergone the most rigorous development but the most widely used is Voice Handicap Index (VHI-30 and VHI-10).

The VHI-30 consists of 30 items which assess the impact of the voice disorder on physical, functional and emotional aspects of the patient's quality of life.[16] The patients rate their perception of their voice problem from 0 (= never) to 4 (= always), giving a possible total score of 120. More recently, the VHI-10 has been introduced.[20] This uses a subset of the VHI-30 items and has shown to have good correlation to the VHI-30 with the advantage that it is quicker and easier to complete.[20] In general, there is good correlation between all the different measures.[24–26]

Mean normative values of total score for the VHI-30 are 6.86 (standard deviation = 9.88) and for the VHI-10 are 2.83 (standard deviation = 3.93).[27] The highest values for the VHI total score are seen in patients with vocal cord palsies, severe structural abnormalities of the larynx and muscle tension dysphonia of origin.[22] For the VHI-30, the threshold value between vocal health and voice dysfunction is considered to be 12 points.[28] A 14-point difference in the total VHI-30 score is considered significant response to treatment, with values rarely returning to normative levels.[22, 24, 29, 30]

Perceptual evaluation of voice

Perceptual evaluation of the voice refers to the process of assessing the characteristics of the voice and grading the severity of specific abnormal features such as hoarseness,

TABLE 62.1 Methods of objective evaluation of voice

Evaluation	Description	Examples
Laryngeal visual assessment	Inspection of the structure and dynamic function of the larynx and rest of the vocal tract together with the vibratory patterns of the vocal folds during phonation	Endoscopic laryngoscopy including stroboscopy, videokymography and high-speed digital imaging (see Chapter 61, Assessment and examination of the larynx)
Quality-of-life measures	Using self-administered, validated disease specific or generic questionnaires to assess the patient's perception of the impact of the voice condition on their quality of life in terms of physical complaints and restriction in participation in daily activities	VPQ, VHI-30, VHI-10, VoiSS, VAAP, V-RQOL
Perceptual evaluation of the voice	Using rating scales to grade the presence and severity of defined qualities of the voice that we can hear such as hoarseness, roughness, breathiness	GRBAS, CAPE-V, VPA
Acoustic analysis	Extracting and objectively evaluating various factors related to the acoustic waveform or spectrum recorded using a microphone placed near the mouth	Fundamental frequency measurements, sound intensity, perturbation measures, spectral measurements
Electrolaryngography / electroglottography	Determined by measuring the changes in electrical conductance between two electrodes placed on the skin over the thyroid cartilage during vocal fold vibration	Fundamental frequency measurements, degree of vocal fold contact, perturbation measures
Aerodynamic measures	Measures of the forces that initiate and maintain vocal fold vibration	Air volume, airflow and subglottal pressure
Voice accumulator	These are means of sampling the voice or aspects of vocal function either over a prolonged period of time or before, during and after a specified vocal stress test	Phonation time, frequency and sound intensity measurements
Combined measures	These attempt to provide a multidimensional measure of voice function	Dysphonia Severity Index, Cepstral Spectral Index of Dysphonia

TABLE 62.2 Patient self-report questionnaires

Patient self-report questionnaire	Abbreviation	Reference
Patient Questionnaire of Vocal Performance	VPQ	Carding and Horsley[15]
Voice Handicap Index	VHI-30	Jacobson et al[16]
Voice-related Quality of Life	V-RQOL	Hogikyan and Sethuraman[17]
Voice Symptom Scale	VoiSS	Deary et al[18]
Voice Activity and Participation	VAAP	Ma and Yiu[19]
Voice Handicap Index-10	VHI-10	Rosen et al[20]

roughness and breathiness.[4, 31] Numerous schemes have been developed (**Table 62.3**) which require the expert listener to rate the voice characteristics using either categorical or visual analogue scales.

The GRBAS (**G**rade, **R**oughness, **B**reathiness, **A**sthenia and **S**train) scheme (**Table 62.4**) is probably the most widely used, partly due to its relative simplicity. Each dimension is rated on a four-point scale where 0 = no perceived abnormality, 1 = mild, 2 = moderate and 3 = severe abnormality. The overall Grade of hoarseness is the most reliable voice quality parameter with Strain and Asthenia (weakness) being relatively poor.[37, 38]

The CAPE-V is a newer measure which replaces the four-point scale with a 100 mm line Visual Analogue Scale. It also encompasses other factors such as pitch and loudness.[36] The Voice Profile Analysis (VPA) scheme is based on a phonetically grounded description of voice quality and is recognized as being a valid and detailed descriptor of voice quality.[7] Many consider it to be too complex for routine clinical use and not a valid tool for assessing outcome.[40]

Acoustic analysis

Acoustic analysis provides quantitative measures based on the voice signal (waveform and spectrum) recorded using a microphone placed near the mouth. The microphone acts as a transducer, converting the acoustic signal into an electrical signal. The amplified electrical signal is most commonly recorded directly to hard disk as uncompressed .wav files. A variety of free and commercial software programmes are available for display, measurement and statistical analysis of the acoustic waveform and spectrum.

TABLE 62.3 Summary of the most common schemes described for perceptual evaluation

Scheme	Abbreviation	Reference(s)
Grade (of hoarseness), Rough, Breathy, Asthenic, Strained	GRBAS	Hirano[32]
Grade (of hoarseness), Rough, Breathy, Asthenic, Strained, Instability	GRBASI	Dejonckere et al[33]
Rauhigkeit (Roughness), Behauchtheit (Breathiness), Heiserkeitsgrad (Hoarseness) method	RBH	Nawka and Anders[34] Nawka et al[35]
Consensus Auditory Perceptual Evaluation of Voice	CAPE-V	ASHA[36]
Vocal Profile Analysis	VPA	Laver[7]

TABLE 62.4 The psychoacoustic and physiological findings associated with each of the five dimensions of the GRBAS scheme[32, 39]

Factor	Psychoacoustic/physiological correlates
Grade (G)	Overall rating of severity of abnormality ('hoarseness') of voice
Roughness (R)	Perceived irregularity in voice Irregular perturbation of pitch and amplitude, noise in low-frequency region and the presence of spectral subharmonics
Breathiness (B)	Audible breath or air escape on the voice Noise below the mid frequencies, incomplete closure of vocal folds resulting in high expiratory flow rate
Asthenia (A)	Weakness or lack of energy in the voice Less harmonic content in the high-frequency region, irregularity of pitch and amplitude, a fading amplitude contour
Strain (S)	Perception of excessive vocal effort Reflects higher pitch, noise in the higher frequencies, increased amplitude of the higher harmonics and increased pitch and amplitude perturbation

VOICE MATERIAL

There are three main types of voice material used in acoustic analysis: sustained vowels, fluent speech and consonant–vowel sequences:[41]

1. **Sustained vowels** have traditionally been used as voice test material in clinical practice for the following reasons:
   - They are the simplest separable components of speech.
   - Although the vowel systems of the world's languages cover a very large range of sound types, three oral vowels are almost universally present so can be used for comparison across studies:[6]
     - a close ('high') front articulation /i/ (as in English b*ee*t)
     - a back ('high') /u/ (as in English b*oo*t)
     - an articulatory open vowel /ɑ/ (as in English f*a*r).
   - Loudness, pitch, intonation and timbre can, to a degree, be separated and controlled for far more readily than for other elements of speech.
   - They predominantly reflect vocal fold vibratory activity.
   - If analysis of phonatory onset and offset are excluded, the stable mid-portion of the utterance is thought to represent the intrinsic quality of a voice which is independent of language.[42, 43]
   - The measurement is quick and easy to perform and has been used in many of the reported clinical studies of pathological voice production.[41]

   Measurements are usually made on a 1000 ms midsection of the sustained vowel, usually /i/ or /ɑ/, produced at a comfortable pitch and loudness.[41] Effort levels and day-to-day variability may influence the results and must be taken into consideration when comparing inter- and intrasubject results.[44]
2. **Fluent speech**, however, has several advantages:
   - It is more directly relevant to the patient's day-to-day experience.
   - It is more related to ordinary voice production, and also to a listener's impression of the speaker's phonatory ability, than sustained vowels.
   - It potentially produces more clinically relevant measures of voice production than sustained vowels.
   - It takes into account the acoustic cues associated with vowel onset and offset, pitch, loudness and intonation control that take place during speech production.

   Two types of speech material are typically used: **read text** and **spontaneous speech**. Read text has the advantage that the same sets of speech sounds are elicited for each recording, allowing cross-clinical comparisons to be made. The disadvantage is that some patients are not able to read aloud or read in a way that is not representative of their fluent spontaneous speech. The most frequently used texts used are *The North wind and the Sun*, 'The rainbow passage', and *Arthur the rat*.[41, 45] Each is phonetically balanced and the choice is largely down to personal preference. Read text and spontaneous speech give

similar but not identical results.[41] Approximately 40 s of a speech sample is needed for perceptual evaluation in order to begin to obtain a useful representation of the main voice characteristics. For electrolaryngography (ELG) measures (see below) and to see the effects of vocal fatigue in more severe cases, 120 s is better.

3. **Consonant–vowel sequences** are also used in two particular situations:
   - For the investigation of rapid voice 'switching' in diadochokinetic sound sequences, the rate (mean number of utterances per second) of repetition of utterances such as alternate voiceless consonants with a vowel, e.g. /pʌ/, /tʌ/, /kʌ/ ('pu-tu-ku') or /pʌ/, /tɜ/, /kɜ/ ('pu-terr-kerr'), can be measured and an assessment made of the accuracy of articulation and rate variability during the task.[41]
   - In the determination of laryngeal airway resistance or indirect subglottic measurement,[46] the sound sequence is a succession of only /pʌ/or /pi-pi-pi/ – the bilabial closure providing a time interval during which intraoral pressure equals that at the glottis.

One caveat when performing any assessment is that it is performed at that point in time and may not reflect the variation in voice quality that is frequently reported by patients. Newer software such as OperaVOX™, which can be set up as an app on a mobile phone or tablet, can allow simple measurements and recordings of the voice to be made by the patient at home at any time of the day.[47] Alternatively, voice accumulators may be used (see below).

MICROPHONES

Accurate measurements of acoustic parameters across the range of vocal frequencies and intensities require a good-quality condenser or electret, omnidirectional, pressure-sensitive microphone.[48] The sound pressure wave radiating from the mouth is converted by the microphone into an electrical signal such that the induced voltage change is proportional to the pressure level. Ideally, it should have a minimum sensitivity of –60 dB and reasonably flat frequency response (i.e. equally sensitive to all audio frequencies) across the range of human hearing (20–20 000 Hz).[12, 41] The microphone-to-mouth distance should be kept constant and the recording system should be calibrated to ensure standardization of recordings.[48, 49] A microphone can be mounted on a headset when it is usually positioned 8 cm from the corner of the mouth. It is usually offset by 45 degrees to avoid overstimulation from the breath stream particularly from plosive sounds.[49] Alternatively, it can be set at a fixed distance (30 cm) from the mouth using either a boom or a lanyard round the neck.[47] Recordings should be done in a quiet room free from extraneous noise.

ACOUSTIC PARAMETERS

Acoustic measures of the voice quantify the physical characteristics of the sound pressure waveform radiating from the lips. There are several parameters that are used in objective measurements based on the fundamental frequency, frequency perturbation (jitter), spectral analysis or sound intensity or combinations thereof. The validity and clinical utility of acoustic parameters as a measure of overall voice quality have been questioned.[50] Many measures have been described[12, 41, 51] but only some of the more common ones in clinical use will be discussed here.

Fundamental frequency

Fundamental frequency is a measure of the rate of vibration of the vocal folds. It is the inverse of the time taken to complete a single vibratory cycle and is measured in cycles per second or Hertz (Hz). It can be measured from short segments (1–2 s) of a sustained vowel made at a 'comfortable pitch and loudness' or from speech (speaking fundamental frequency (SFF)). It can be measured from either the acoustic (F_0) or the ELG (F_x) signal (see below). The reliability of the automatic F_0 calculation from the acoustic signal, however, worsens with increasing severity of the dysphonia.[12] In males the SFF drops from young adulthood into middle age and rises again in old age. In women the SFF remains fairly constant from 20–50 years and then drops.[41]

$$\text{Fundamental frequency } (F_0) = \frac{1}{\text{time to complete one vibratory cycle}}$$

Sound intensity and sound pressure level (SPL)

The amplitude of the signal relates to its sound pressure or strength. As a listener we perceive this as loudness. In practice, sound intensity is measured in terms of the logarithmic ratio of the absolute sound pressure to a reference sound pressure level (SPL) expressed in decibels. This means that doubling the sound pressure raises the SPL by 6 dB. For a more in-depth discussion see Baken and Orlikoff[41] and Speaks.[52]

Speech intensity levels for sustained vowels are quite different from connected speech due to the physiological and linguistic pauses in the latter causing marked fluctuations in pressure. Comparison of results published in the literature are extremely difficult due to the lack of standardization of the measuring techniques.[41] The mean SPL for a read text passage of connected speech produced at a comfortable phonation level by healthy subjects is approximately 70 dB measured at 30 cm from the mouth. However, the intersubject variability is approximately 20 dB for men and slightly less for women and the intrasubject variability for repeated measurements is approximately 3 dB.[53]

Jitter and shimmer

It is normally possible for an individual to produce a vowel sound for several seconds with little variation (perturbation) in the frequency (jitter) or intensity (shimmer). Pathological voice samples have been shown to have higher

levels of jitter and shimmer than normal[41, 51] although, for jitter, these have not been universal findings and the validity and reliability of these measures has been questioned, particularly in severely dysphonic voices.[54–56] Although widely used as 'objective' measures of voice, there is poor correlation between perceived vocal quality and acoustic measures of jitter and shimmer.[57, 58] This is mainly due to the perceptual difficulties of isolating jitter and shimmer as separate dimensions and from the spectral noise in the voice. In addition, there are many different ways of calculating jitter and shimmer, which adds to the confusion. For a detailed discussion on these perturbation measurements see Baken and Orlikoff.[41]

Voice range profile (phonetogram)

A voice range profile (VRP) or phonetogram is a visual display of the dynamic range of the voice in terms of frequency and vocal intensity[59] and has been used in both adults and children.[60, 61] It is usually produced by recording the patient's ability to produce sustained vowels (usually 10 continuous, periodic cycles of an /a/ vowel[62] across their frequency range at the quietest and loudest note they can produce.[60] Experience in performing the procedure to a given protocol is extremely important.[63–65] The features of interest are the overall shape, loudness and frequency ranges and phonatory area.[59, 64] It is of particular value in determining and documenting areas of difficulty in the singing voice[66] and for demonstrating improvement in the dynamic range of the voice following treatment of voice disorders.[67] It is not widely used in the UK as it is time-consuming to perform but it is commonly performed in many European phoniatric departments.

Spectrogram and long-term average spectrum

The acoustic output of the vocal tract resulting from the interaction of the vocal fold vibration with the vocal tract can be displayed graphically in a 3D way in what is known as a spectrogram. Time from beginning of the vowel utterance to the end is displayed on the *x* axis. A logarithmic display of the frequency distribution is seen on the *y* axis while the amplitude or amount of energy in the spectrum for a given frequency or frequency band is represented by increasingly dark shades of grey.

There are two forms of spectrogram: narrow-band and broadband (or wide-band) spectrograms. The narrow-band spectrogram (**Figures 62.1a** and **62.2a**) displays the concentrations of energy in each harmonic across the frequency range. The number of harmonics displayed is largely determined by the loudness of the voice and the abruptness of vocal fold closure (see below). The broadband spectrogram, on the other hand, gives more information about the how the 'groupings of the harmonics' (formants) are arranged (**Figure 62.3a,b**).[41, 68] The most dense and central parts of these broadband spectrograms (i.e. those with the greatest energy or amplitude) are taken to represent the resonant frequencies of the vocal tract.

Linear predictive coding (LPC) and fast Fourier transform (FFT) are automated and mathematical ways of picking out and displaying these formant peaks (**Figure 62.4**).[41] Although it is probably more reliable overall to pick out the formant frequencies by hand, these automated techniques provide a useful quick alternative. They are not always reliable, particularly if the signal changes abruptly, the F_0 is too high (above 350 Hz) and if there are significant anti-resonances, i.e. when there is significant nasalization of the speech sound.[41]

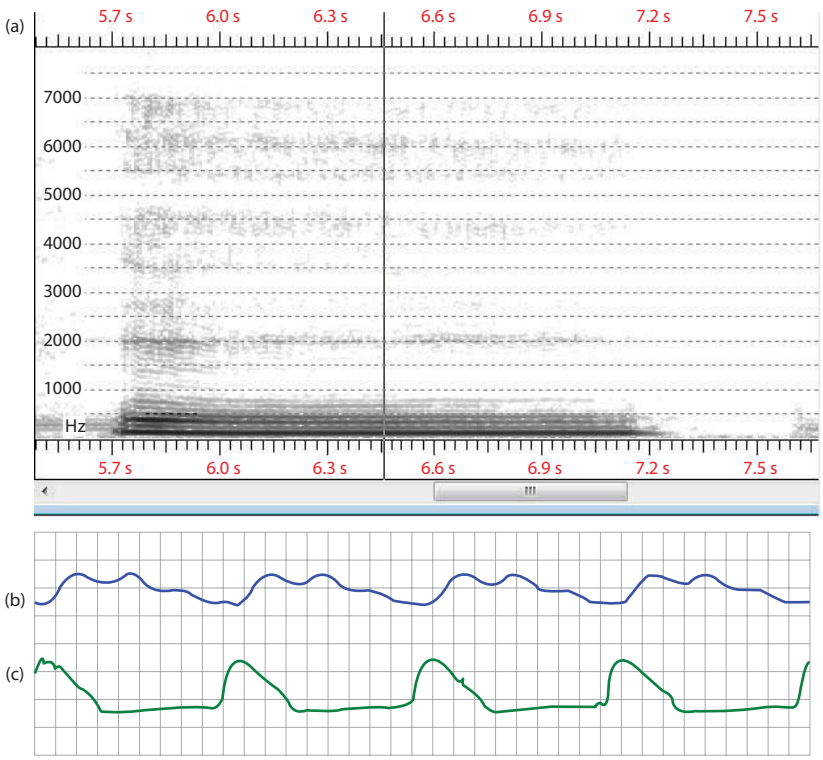


Figure 62.1 Sustained /i/ vowel produced at 109 Hz by 53-year-old male patient with left recurrent laryngeal nerve palsy pre-thyroplasty. (a) Narrow-band spectrogram showing poorly defined harmonic structure and ill-defined high-frequency band (5500–7000 Hz) due to breathiness of voice; **(b)** speech (acoustic waveform) and **(c)** ELG waveform at the point in utterance indicated by the vertical line on the spectrogram. Note the short contact quotient on the ELG waveform (mean Qx: 28.25%) associated with poor vocal fold contact.

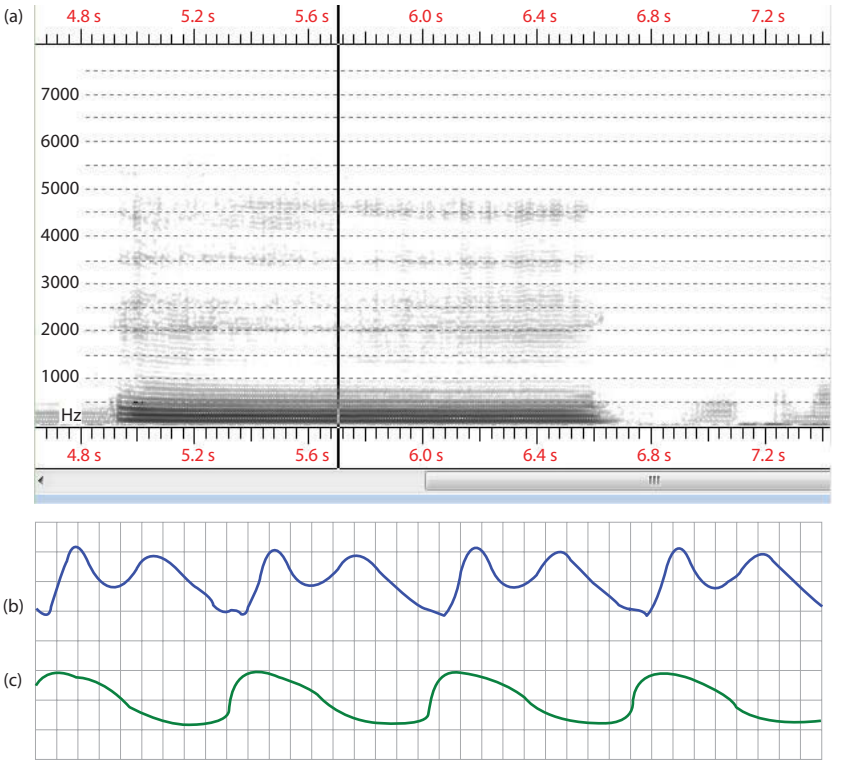


Figure 62.2 Sustained /i/ vowel produced at 106 Hz by same patient as in Figure 62.1 post-thyroplasty. (a) Narrow-band spectrogram showing better-defined harmonic structure particularly and beginning and end of utterance and loss of high-frequency noise component (5500–7000 Hz); **(b)** speech (acoustic waveform) and **(c)** ELG waveform at the point in the utterance indicated by the vertical line on the spectrogram. Note the improved contact quotient on the ELG waveform (mean Qx: 48.16%) associated with better vocal fold contact from the medialization procedure.

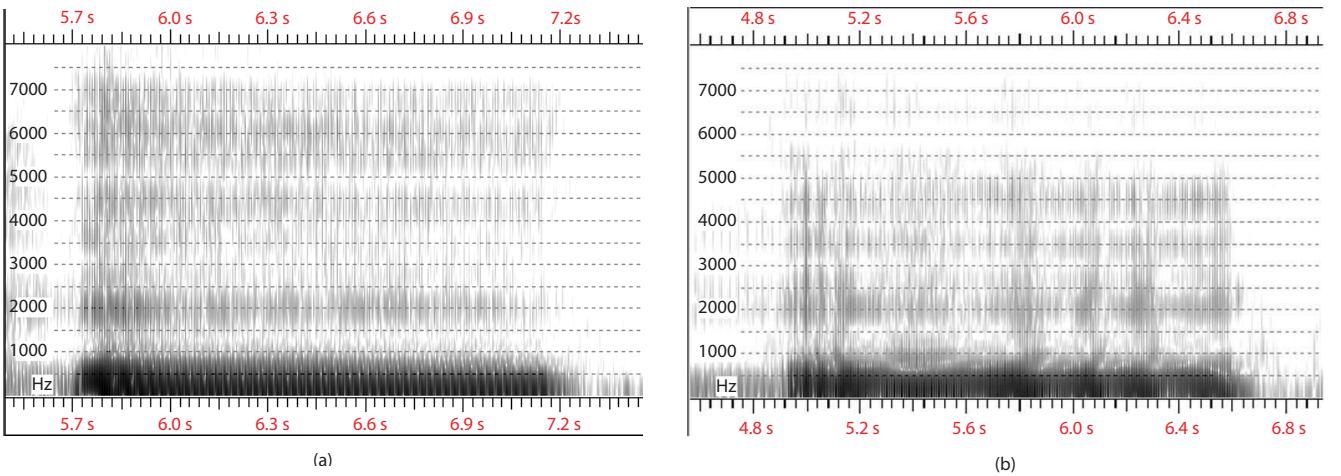


Figure 62.3 Broadband equivalents from Figures 62.1a and 62.2a for sustained vowel /i/. Neither shows really strong banding (except for first formant) but pre-thyroplasty shows more noise in signal in general, particularly at higher frequencies.

A different way of displaying these data is to look at the average amount of energy at each frequency for a given time period. The averaged relative amplitude of the sound level in dB is displayed on the *y* axis against the frequency range on the *x* axis. The display is known as a long-term average spectrum (LTAS) (**Figure 62.5**). Some workers consider LTAS a potentially good index of voice quality.[41, 69] Depending on the nature of the sound, for a given F_0 the strength or amplitude (amount of energy) of the harmonics changes as the frequency increases and the rate of change is known as the spectral slope (usually measured in dB/octave). Vocal fold closure occurs much faster than vocal fold opening and it is this abrupt closure that largely determines (i) the amount of energy in the acoustic spectrum, (ii) the overall number of harmonics produced and (iii) the energy in the high frequencies. This abrupt closure results in a voice which is perceived as 'bright' and which projects well. It is associated with a slowly reducing spectral slope. Conversely, incomplete or slow vocal fold closure results in less energy in the 'acoustic spectrum' and fewer higher harmonics. This means less energy is radiating from the lips and will result in a steeper spectral slope. The voice may be perceived as breathy and will not project well, which, in more extreme cases, can make the sound pattern unrecognizable or inaudible.[41]

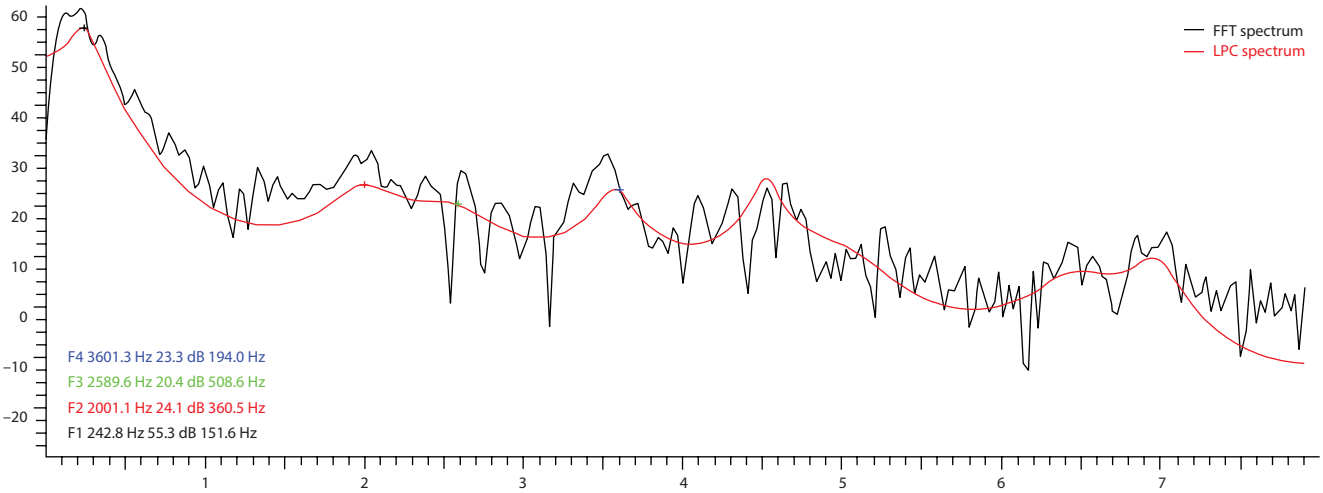


Figure 62.4 Formant frequency identification for post-thyroplasty patient on sustained British English /i/ vowel using linear predictive coding (LPC) and fast Fourier transform (FFT). Values F1–F4 represent the respective formant frequencies (Hz), amplitude (dB) and bandwidth (Hz).

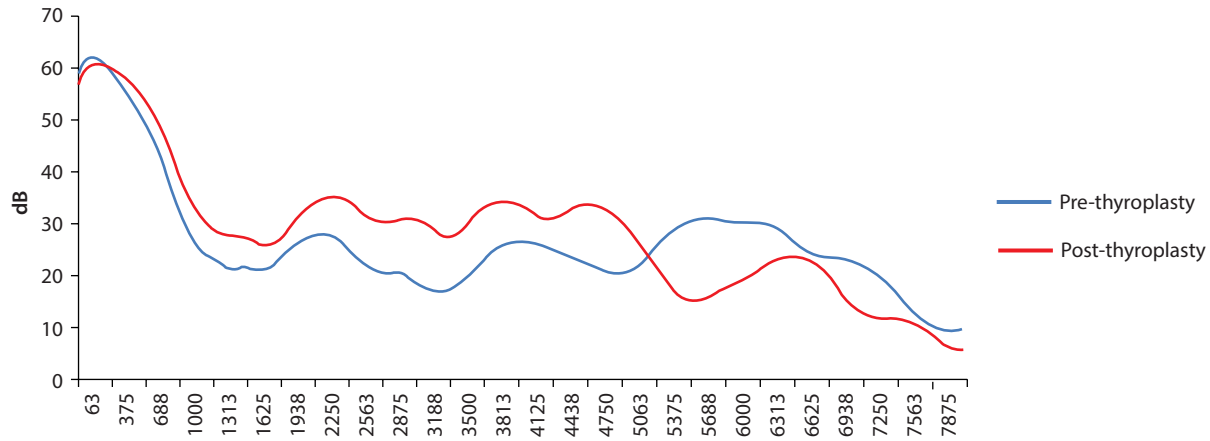


Figure 62.5 Broadband long-term average spectra (LTAS) for a patient with recurrent laryngeal nerve palsy on sustained vowel /i/. This is a graphical display of the spectral information in Figure 62.3 showing improvement in formant frequency energy and a reduction in noise element in the 5500–7500 Hz range before thyroplasty (blue) and following surgery (red).

Measurements of spectral noise energy versus harmonic energy

Speech and voice have two components: a well-defined periodic signal that has a clear harmonic spectrum and an additional source of random 'spectral noise'.[70, 71] Spectral noise is inherent in normal as well as pathological voice and increases with the openness of the vowel. For example, it is greater for vowels such as /œ/ (as in b*a*d) and least for /u/ and /i/ (as in b*oo*t and b*ee*t respectively).[72] Increasing vocal effort and lower pitches are associated with an increase in spectral noise and there is a reasonable correlation (0.74–0.92) between spectral noise and the perceived roughness of a vowel.[73] The noise element can be generated from irregular (aperiodic) vibration of the vocal folds or some other structure within the vocal tract (e.g. the false cords) and/or turbulent airflow (e.g. air leakage through an incompletely closed glottis).

The commonest measures used in clinical practice are the harmonics-to-noise ratio, normalized noise energy and the signal-to-noise ratio (see below). Unfortunately, these measures do not distinguish between pathological changes as a result of turbulent noise and irregular glottal excitation.[74, 75]

Harmonics-to-noise ratio The harmonics-to-noise ratio (HNR) (measured in dB) is the mean intensity of an average waveform (noise-free) divided by the mean intensity of the isolated noise component for the series of waveforms in the utterance.[41, 76] The greater the noise, the lower the HNR (**Table 62.5**). Some authors report higher normative and post-treatment values.[41]

$$\text{Conceptual HNR dB} = 10^{*}{}_{\log 10}\frac{\text{energy contained in the harmonics alone}}{\text{energy in the noise alone}}$$

The correlation between the HNR and perceptual evaluation has varied considerably between studies. Yumoto et al[76] found a correlation between hoarseness and HNR of 0.849 but Wolfe et al[77] noted a –0.32 correlation with a seven-point

TABLE 62.5 Some examples of HNR values for /α/ (as in *far*) vowel in normal, dysphonic and treated patients. There was no statistical difference between men and women[76]

	Mean (dB)	SD	Range (dB)
Normal (*n* = 42)	11.9	2.32	7.0–17.0
Pre-op dysphonics (*n* = 18)	1.6		–15.2–9.6
Post-op (*n* = 23)	11.3	3.13	5.9–17.6

severity of dysphonia score. It has been found to be an excellent predictor of breathiness[78] but tends to overestimate the noise energy in the presence of jitter and shimmer.[75, 79]

Normalized noise energy Normalized noise energy (NNE)[80] assesses the relative level of vocal noise to that of harmonics but bases the analysis on a relatively small number of vocal periods (as opposed to individual cycles as in the HNR). This has the advantage that it avoids the effects of drift in fundamental frequency or intensity during the utterance, which can be a problem in the calculation of the noise component of the HNR. Like other acoustic measures, the degree of effort used in producing the voice sample, day-to-day variability[44] and algorithms for calculating the noise energy in the signal can all influence results[41] so care must be taken when comparing studies. The higher the negative value, the better the voice. NNE has been shown to correlate with perceived breathiness in dysphonic children.[81] A few studies have been published where it has been used as an outcome measure and to distinguish pathological from normal voices.[82–85]

Signal-to-noise ratio The signal-to-noise ratio (SNR) is an alternative approach that avoids the need for harmonic analysis yet effectively achieves the same end result.[86] The underlying concept is that, since noise is random, its average is zero and the average amplitude will be an essentially noise-free estimate. Subtraction from the raw signal then leaves the noise alone. A ratio higher than 1:1 (greater than 0 dB) indicates more signal than noise. The process depends, however, on the assumption that the voice signal is truly periodic.

$$\text{S/N dB} = 20^{*}_{\log 10} \frac{\text{average amplitude of mean vocal fold cycle}}{\text{average of difference between mean and raw cycles}}$$

In practice it is difficult perceptually to distinguish between the sensations associated with the following:

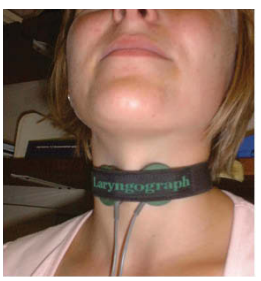
- frequency irregularity from cycle to cycle of vocal fold vibration
- amplitude irregularity from cycle to cycle
- the presence of random noise in the voice.

Electrolaryngography

The electrolaryngograph (ELG) consists of two electrodes placed on the skin on either side of the thyroid cartilage. A high-frequency current (3 megahertz) is applied between the two electrodes and held at a constant voltage. Vocal fold vibration changes the electrical conductance between the electrodes. The resulting waveform can be analyzed automatically to obtain measures of the rate of vocal fold vibration (fundamental frequency, Fx) and frequency perturbations (e.g. jitter). Experimental data have also shown the waveform can be used to measure indirectly variations in the contact area between the mucosa of the two vocal folds during a vibratory cycle (**Figure 62.6**, and see **Figures 62.1c** and **62.2c**).[90] As the ELG signal is a simpler waveform which is unaffected by resonances of the vocal tract, it provides one of the most accurate methods of determining the fundamental frequency, even in severely dysphonic voices. However, it is not always possible to detect a waveform, particularly when the soft tissues of the neck are thick.

SPEAKING FUNDAMENTAL FREQUENCY AND F_0 RANGE

Mean speaking fundamental frequency (SFF) can be measured from a 2-minute sample of speech and can be plotted as a frequency histogram (**Figure 62.7**) to give a graphical representation of the dynamic frequency range of the voice. In the Speech Studio (Laryngograph Ltd) programme, for example, frequency measurements are displayed on a logarithmic scale which is divided into 120¼ tone 'bins' between 27.5 Hz and 440 Hz. These frequency 'bins' correspond well to perceived pitch and tend to bias the higher frequencies. In addition, a second frequency histogram (DFx2) can be overlaid on the graph. This counts the 'pitch-pairs' (i.e. when two consecutive periods differ by no more than 10%) and represents the minimum number of consecutive vibratory cycles that can potentially be perceived as periodic. Poor voice quality is in



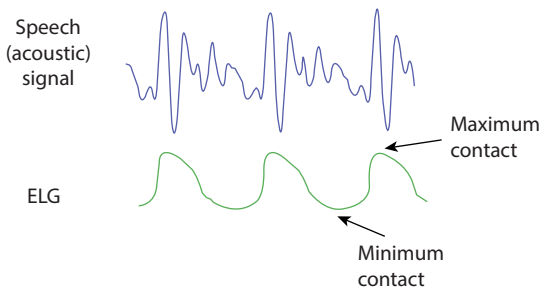


Figure 62.6 **(a)** Laryngograph® electrodes placed over thyroid cartilage. **(b)** Speech (acoustic) waveform acquired using a tie clip or head-mounted microphone. **(c)** The ELG waveform reflects the variation in conductance between the electrodes during phonation. In modal voice the vocal folds close more rapidly than on opening, giving a sharper rise in the waveform.

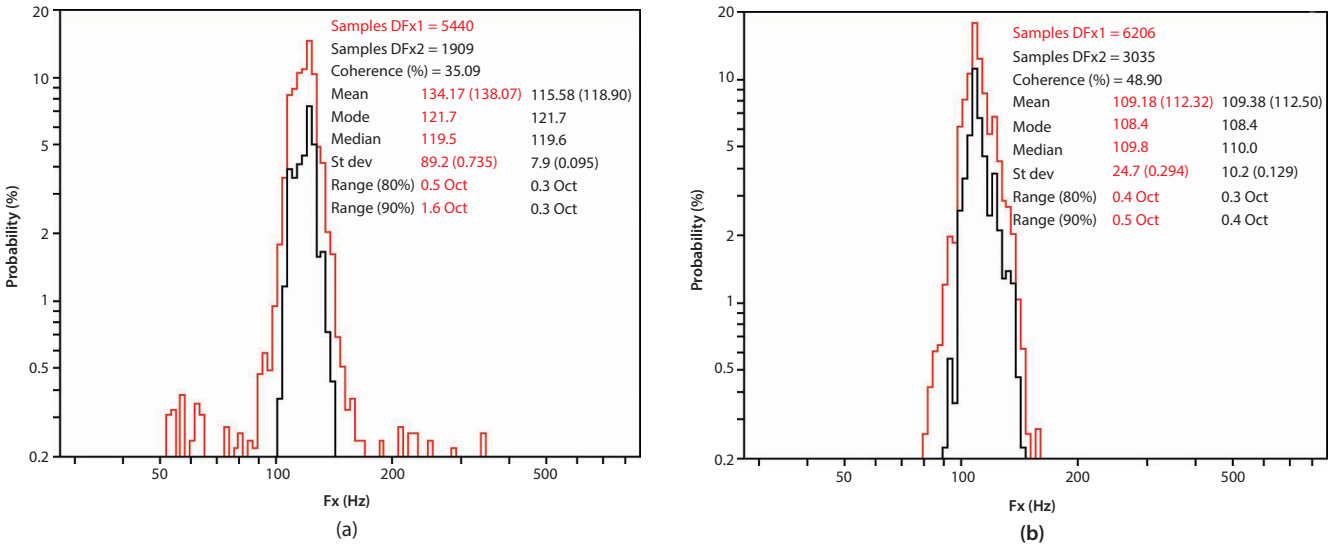


Figure 62.7 DFx1 and DFx2 frequency histograms (a) pre-thyroplasty and **(b)** post-thyroplasty. DFx1 demonstrates the relative number of times the vocal folds vibrated at a certain frequency (or more precisely frequency bin, see text) during the reading of a passage of text. The DFx2 demonstrates 'pitch-carrying pairs' indicating smooth vibratory frequency change associated with good quality voicing. In general, the closer the DFx1 and DFx2 distributions are graphically, the better the quality voice. This can be quantified in terms of percentage coherence value.

TABLE 62.6 Example of normative data based on a total of 43 female and 14 male Portuguese subjects with no self-reported voice problems (including smokers)[89]

	Men		Women	
Mean	**Reading**	**Conversation**	**Reading**	**Conversation**
Mean SFF (Hz)	109.6	109.2	190.3	186.6
Dynamic frequency range DFx1 90% (octaves)	0.75±0.18	1.18±0.49	0.86±0.22	1.12±0.48
Irregularity score (CFx)%	12.5±7.3	23.5+/–15.6	7.6±5.2	12.3±7.4
Mean contact quotient (Qx)%	45.9	46.3	44.1	43.8
Standard deviation of contact quotient (Qx)%	5.9	7.5	6.1	7.3

general associated with poor correspondence between the DFx1 and DFx2 histograms (**Figure 62.7b**) and reflected in a reduced coherence percentage value. Various parameters can be measured, such as the mean, mode and median SFF and the 80% and 90% ranges. Rather than absolute values, the range in octaves is perhaps more meaningful. Examples of normative values for vocally healthy individuals are given in **Table 62.6**.

$$\text{Coherence \%} = \frac{\text{Number of samples DFx2}}{\text{Number of samples DFx1}}$$

A lower than average mean SFF is found in conditions that increase the mass per unit length of the vocal fold mucosa such as Reinke's oedema[91, 92] and hypothyroidism.[93, 94] A higher than average SFF is seen in puberphonia,[95, 96] scarring of the vocal folds, laryngeal cancer[97] and in some cases of recurrent laryngeal nerve palsy.[98]

A restricted frequency range is found in both organic conditions of the vocal folds, neurological conditions such as Parkinson's disease[99, 100] and psychological conditions including depression and, to a lesser extent, schizophrenia.[101, 102] Some patients also find empirically that by restricting their frequency range they can maintain a reasonably stable vocal fold vibratory pattern and voice quality. An extended range with good correspondence between DFx1 and DFx2 indicates an exaggerated use of the dynamic range of the voice. In contrast, a large range with poor correspondence suggests poor control over vocal fold vibration and is associated with perceptually severe dysphonia.

PERCENTAGE IRREGULARITY SCORE (CFx)

Plotting frequencies of successive vocal fold vibrations against each other during running speech (approximately 120 s) should result in a well-defined single diagonal distribution for normal voice. In pathological voice, such as a recurrent laryngeal nerve palsy, the ability to control cycle-to-cycle variation in frequency is impaired, resulting in deviation from the diagonal line (**Figure 62.8**). This deviation can be quantified by measuring the number

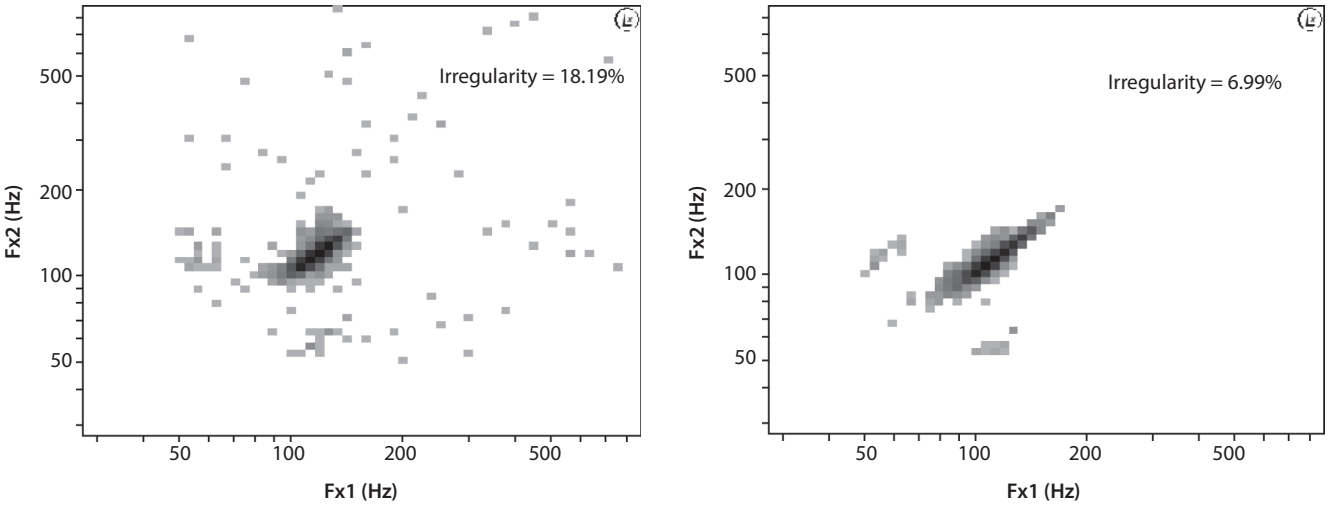


Figure 62.8 CFx1 distributions (a) pre- thyroplasty and (b) post- thyroplasty. This demonstrates the cycle-by-cycle change in frequency of vibration of the vocal folds. The better the voice the straighter and less scatter from the diagonal. This can be quantified in terms of a percentage irregularity score.

of data points straying ±3% away from the diagonal and expressing this as a percentage of the total number of data points registered. It can be seen that the CFx percentage irregularity score values for normal individuals in **Table 62.6** (which include smokers) are greater for males and for conversational voice. For the pre- and post-operative examples in **Figure 62.8** the irregularity scores are 18.9% and 6.99% respectively.

CONTACT QUOTIENT MEASUREMENT (CQx)

As well as frequency measurements it is also possible to derive information about the degree of contact between the vocal folds during the vibratory cycle from the ELG waveform. This can be expressed as a percentage of time to complete one vibratory cycle.

$$\text{Percentage contact quotient Qx} = \frac{\text{Lx closure width 70\% down from positive peak}}{\text{time to complete one vibratory cycle}}$$

There appears to be a positive correlation between contact quotient and vocal intensity for sustained vowels.[103, 104] The contact quotient increases with the level of vocal training[105, 106] but also in pathological conditions when the mass of the vocal folds is increased, such as Reinke's oedema and certain types of muscle tension dysphonia where the voice is pressed. Reduced contact quotients are usually found in cases of vocal fold palsy and paresis (**Figure 62.9**) and in some cases of presbylaryngis and muscle tension dysphonia associated with weak, breathy or asthenic voices. The standard deviation of the contact quotient is generally increased in dysphonic patients,[89] reflecting the increased difficulty in controlling the degree of contact in speech tasks.

Aerodynamic measures

Clinically there are three main factors that can be measured which are of interest in voice production: air volume, air flow and subglottic pressure.[107]

AIR VOLUME

Tidal volume (5–6 L) is a usable part of total lung capacity (6–7 L). In quiet respiration we use only 10–15% of the tidal volume but the full amount can be used for respiration or voice in demanding physical activities, such as exercise or singing. Actual lung volumes are in themselves not particularly informative in speech science but the changes in air volume during speech (airflow) are of much more potential interest.[41] Body plethysmography remains the gold standard for obtaining measurements of changes in air volume during speech or singing but is only used in research settings. Alternative approaches, again only really used in research, are to use magnetometers and inductance plethysmographs placed over the chest and abdominal walls, although the accuracy of these techniques has been questioned.[41, 108] As flow is essentially the change in volume over time, there are two alternative methods of deriving flow and volume measurements from a single transducer:

- by mathematically integrating the oral airflow signal from a pneumotachograph[107]
- by differentiation of the output of a volumatic device such as a spirometer.[41]

In clinical practice where this is undertaken, the pneumotachograph is more commonly used. The main drawback, however, is the interference with speech and change in vocal resonance due to the face mask.[107]

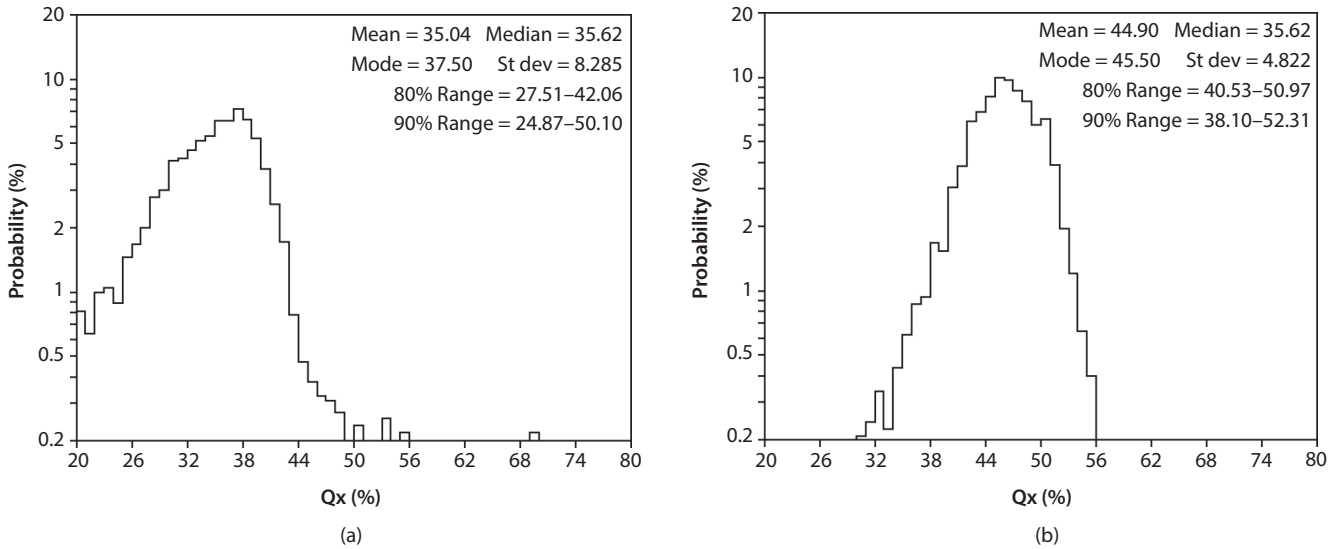


Figure 62.9 DQx1 data (a) pre-thyroplasty and (b) post-thyroplasty. The change in percentage contact with each cycle of vibration is displayed as a probability histogram. The improvement in contact quotient following surgery is seen with a return to normal mean and modal values.

AIR FLOW

Airflow associated with phonation is usually specified in terms of volume velocity (litres per second). It can be used to measure:

- flow during sustained phonation to provide an indicator of functional efficiency of the laryngeal system
- flow associated with consonants to evaluate oral articulatory events
- nasal airflow to assess the velopharyngeal function.[41]

Only the important measures associated with the first use will be discussed here:

Mean airflow rate, Vocal Velocity Index and glottal flow waveform

- The **mean airflow rate** (**MFR**) is the volume of air displaced during phonation on a sustained open vowel such as /œ/ (as in b*a*d) divided by the time taken to produce the phonation.[32] It is usually measured using a facemask or mouthpiece to channel air through an airflow transducer such as a pneumotachograph.[41]
- The **Vocal Velocity Index** (**VVI**) is a variant designed to provide a degree of flow comparison normalization between different-sized speakers.[41, 109] It is calculated by dividing the MFR by the speaker's vital capacity. Normal values for a range of British speakers have been reported.[41, 109] Laryngeal disorders are often associated with excessive air escape and consequently increased MFR and VVI.[41] Conversely, where glottal contact is excessive in conditions such as spasmodic dysphonia, these values are reduced.[41, 109] Both the MFR and VVI have been used as objective outcome measures following treatment.[41]
- The **glottal flow waveform** or **flow glottogram** is a representation of the airflow during each glottal cycle. It is derived from the oral airflow signal through a special pneumotachograph placed in a circumferentially vented facemask using a technique known as **inverse filtering**.[41, 107] From this, values such as peak flow (L/sec), AC flow (L/sec), minimum flow (L/sec) and maximum flow declination rate (L/sec/sec) can be derived. It is used mainly as a research tool.

Maximum phonation time, phonation quotient and s/z ratio

- **Maximum phonation time** (**MPT**) is measured by asking the subject to inhale as deeply as possible and then sustain a steady /ɑ/ vowel (as in f*a*r) for as long as possible.[32, 41] The longest of three repeated measurements is selected. Values under 10 s are regarded as pathological.[32] It is a simple tool used widely in clinical practice as an indicator of the severity of the dysphonia and as an outcome measure, but its reliability has been questioned.[41] It does not allow distinction between poor glottal closure from reduced pulmonary function and vocal cord abnormalities such as a recurrent laryngeal nerve palsy.[41]
- The **phonation quotient** is defined as the vital capacity divided by the MPT.[41] It provides some correction for the size of the speaker's movable air supply on maximal vowel duration in a similar way to the VVI. Although it correlates with the MFR, it is less sensitive and is of questionable clinical value.[41]
- The **s/z ratio** is a variation of the MPT whereby the maximum sustained time for a speaker to make both an /s/ and /z/ sound are recorded.[41, 110] A normal speaker can usually maintain the sound for approximately the same amount of time for both the voiceless /s/ and voiced /z/ consonant, giving a ratio of approximately 1 : 1. Abnormalities which interfere with vocal fold vibration or which affect glottic closure would be expected to reduce the /z/ value but not have any significant effect on the /s/ time, thus increasing the ratio.

Although this simple test is used quite widely in clinical practice, some of the original precepts have been challenged as it depends on eliciting a maximum performance in a speaker. Subsequent studies have shown that there is a wide range in normal values and its sensitivity and utility are therefore questionable.[41]

MEASURES OF SUBGLOTTIC PRESSURE

The vocal folds will only vibrate when the air pressure in the subglottis overcomes the tissue resistance of the vocal folds. The **phonation threshold pressure** is the minimum subglottal pressure required to induce oscillation.[111, 112] Low-frequency phonation threshold pressure has been measured at 0.3–0.4 KPa and generally increases with the frequency of vibration, increased tissue viscosity (stiffness) and increased glottic/false cord constriction.[111, 113–115]

Normal values of **subglottic pressure** during habitual phonation are in the range of 0.5–1.0 KPa[32] and there is a positive correlation with intensity.[41] Subglottic pressure is potentially an important clinical value to measure as failure to generate an adequate, stable level can result in abnormal speech intensity levels or sudden shifts in the fundamental frequency.[116] An inadequate subglottic pressure can result from chest disease (lung parenchyma or thoracic wall), laryngeal disease or neuromuscular conditions that affect the laryngeal resistance (e.g. vocal fold palsy).[41] Excessive subglottal pressures are seen in hyperfunctional voice conditions when the voice is pressed and in adductor spasmodic dysphonia.[117, 118]

Unfortunately, subglottic pressure during phonation is not easy to measure. The most accurate direct method is to place a pressure-sensing device in the subglottis. This can be achieved by performing a percutaneous cricothyroid or tracheal puncture with a large-bore hypodermic needle and attaching it to a pressure transducer.[118] Alternatively, a very small-pressure transducer can be inserted via the nose and positioned directly in the subglottis.[32, 41] Both these direct methods are invasive and used only in research studies. An alternative, more practical clinical method is to estimate the subglottic pressure by measuring oral pressure during the production of a sound sequence such as /pi-pi-pi-pi-pi/ at a constant rate, pitch and loudness.[119] During the production of /p/, vocal folds are abducted and the peak intraoral pressure is essentially equal to that throughout the airway including the subglottis. An estimate of the average subglottal pressure during vowel production can be obtained by measuring pressure at the midpoint of a line connecting two successive pressure peaks.[107, 120] Care must, however, be taken in the interpretation and extrapolation of the results from this very specific speech task into connected speech.[115, 120]

Voice accumulators

'Voice accumulators' are wearable voice-monitoring systems which can provide reliable and objective measures of voice use during daily activities away from a clinic environment. They can potentially provide a better understanding of the role of daily voice use in the causation of voice disorders. Most contemporary devices are based on contact microphones or accelerometers placed at the base of the neck. Recording vocal fold activity rather than the voice allows a degree of privacy to the wearer and efficiency in post-acquisition processing.[121] This relatively new technology can provide data on the proportion of the time spent using the voice (phonation time), fundamental frequency, sound intensity measurements and potentially estimates of airflow.[122] They are used mainly as research tools at present.

Combined measurements

There is an intrinsic attraction in combining multiparameter measures of voice function to help discriminate between normal and pathological voices. Several schemes have been developed[123, 124] and, of these, the Dysphonia Severity Index (DSI) is probably the most widely used, especially in Europe.

DYSPHONIA SEVERITY INDEX

The DSI is a single quantitative measure that has been derived by multivariate analysis from 387 dysphonic subjects.[123] It is calculated by summing four weighted aerodynamic and acoustic factors as follows:

+ Maximum phonation time (seconds) × 0.13

+ highest frequency (F0) achievable (Hz) × 0.0053

− lowest intensity (dB) × 0.26

− jitter (%) × 1.18

+ 12.6 (correction factor)

= DSI score

In the original study a perceptually normal voice gives a maximum value of +5 while lesser values (to a maximum of −5) represent worsening degrees of dysphonia.[123] A more recent study suggests that +8 to −8 may be more practical.[125] A reduction of the DSI score by 2.5 is accepted as a clinically significant therapeutic outcome although this value has been challenged.[126, 127] The inverse DSI score has also been shown to correlate well with the VHI total score.[123] However, the component measures of the DSI may be prone to variability that may affect the stability of the DSI itself.[126, 127] There is some test–retest variability in normal subjects.[126, 127]

FUTURE DEVELOPMENTS IN VOICE MEASUREMENT

It is likely that laryngostroboscopy will remain the most useful clinical tool in the evaluation of voice disorders for the foreseeable future as the image quality continues to improve. Although currently expensive, the CCD

chip nasoendoscopes (videoscopes) overcome the main problem of poor image quality currently obtainable with many video fibre-optic systems. Patient self-rated questionnaires will remain an important determinant of patient's perception of the impact of the voice disorder (and therapeutic intervention) on their quality of life. Given the complexity of voice, the huge range of normality and 'normal' inter- and intrasubject variability, it is unlikely that any single acoustic, aerodynamic or other measure will be sensitive and specific enough to characterize a given type of voice disorder. It is hoped that advances will continue to be made in the use of analysis of connected speech and multiple combined measures which may lead to a better profile of the vocal capabilities of the individual. Understanding and measuring the variability in patients' voices with use and in different environments with voice accumulators may also allow better targeted treatment. The constraints of patient tolerance, clinical time and cost will also play an important part in determining which tests are acceptable in clinical practice. The patient's perception of their impairment, limitation in activity and participation restriction should remain the prime motivator for deciding on the need for treatment once serious laryngeal disease has been excluded.

KEY POINTS

- Speech, voice and phonation are terms with specific definitions.
- Abnormal vocal fold vibration results in dysphonia whilst an absence of vocal fold vibration results in aphonia.
- Normal voice production requires a pressure gradient across the vocal folds, appropriate vocal fold structure mass and elasticity and a resonating chamber of variable size and shape (the vocal tract).
- Health-related questionnaires (specific and generic), Perceptual Evaluation, Acoustic Analysis and Electrolaryngography are all used to measure voice quality.

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CHAPTER 63

STRUCTURAL DISORDERS OF THE VOCAL CORDS

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SEARCH STRATEGY

Data in this chapter may be updated by Medline, Embase and the Cochrane Library searches using the keywords: voice disorders, vocal cords, structural, lesions, polyps, nodules, varices, haemorrhage, sulcus, cyst, inflammatory, reflux, muscle tension, dysphonia and Reinke's oedema. Unfortunately, there have been very few good quality, randomized, controlled studies in this area and most of the evidence is level 2–4.

INTRODUCTION

The larynx is a complex organ in the upper aerodigestive tract with multiple functions. Because of its location, any disease condition affecting the larynx may present with symptoms including hoarseness, breathing or swallowing difficulty and aspiration pneumonia; multiple symptoms are often seen. This chapter discusses a comprehensive approach to evaluation of the patient presenting with an altered voice.

ASSESSMENT AND EVALUATION

The assessment and evaluation of patient with voice disorder should ideally be done in a multidisciplinary clinic by a laryngologist and a speech therapist. A voice coach may be part of this team depending on the case mix in the clinic and if the clientele includes a large number of professional singers. This recommendation is not prescriptive but an example of best clinical practice.[1]

History

Assessment of a patient with laryngeal disorders should start with a detailed history. Often one may be able to establish the diagnosis from the history alone. The patient should be allowed to present his/her story in his/her own words without interruption at first. Some voice disorders are diagnosed entirely by listening to the patient's voice (spasmodic dysphonia, functional dysphonia) and after excluding other conditions by physical examination of the larynx.[2] There are different terminologies that the laryngologist may use in describing voice symptoms. These must be explained to the patient in simple terms. Examples of terminology used to describe voice symptoms are:

Dysphonia: Any impairment of the voice or difficulty speaking.
Dysarthria: Difficulty in articulating words, caused by impairment of the muscles used in speech.
Dysarthrophonia: Dysphonia in conjunction with dysarthria, for example after a cerebrovascular accident, head injury or part of a degenerative neurological condition, such as motor neurone disease.
Dysphasia: Impairment of the comprehension of spoken or written language (sensory dysphasia) or impairment of the expression by speech or writing (expressive dysphasia), especially when associated with brain injury.
Hoarseness: A perceived rough, harsh or breathy quality to the voice.
Odynophonia: Pain when talking.

Generally speaking, the term dysphonia is interchangeable with hoarseness but most patients understand the term husky voice better. Very often, the voice symptom is not just a single entity but a description of how the voice is perceived by the patient, or their impression of how other people perceive their voice. It is therefore useful to use self-administered questionnaires and perceptual rating of voice questionnaire to assess the voice. These tools will not only help the laryngologist understand the severity of

the voice problem but also help in measuring outcomes after treatment. Commonly used measures are:

- GRBAS – Grade, Roughness, Breathiness, Astenia and Strain[3] (**Box 63.1**)
- VoiSS – Voice Symptom Scale[4] (**Box 63.2**)
- VHI-10 – Voice Handicap Index[5] (**Box 63.3**)
- RSI – Reflux Symptom index[6] (**Box 63.4**).

A normal voice is difficult to define (see Chapter 62, Evaluation of the voice). Although we normally think of a disordered voice as one that is hoarse, this is not always the case. It may only cause problems when certain demands are placed upon it. A disordered voice can be defined as one that has one or more of the following characteristics:

- It is not audible, clear or stable in a wide range of acoustic settings.
- It is not appropriate for the gender and age of the speaker.
- It is not capable of fulfilling its linguistic and paralinguistic functions.
- It fatigues easily.
- It is associated with discomfort and pain on phonation.

Voice disorders are often multifactorial in aetiology and, to complicate matters, patients may develop compensatory vocal behaviours to be able to communicate effectively. This may mask the true underlying or primary disorder, such as muscle tension imbalance secondary to

BOX 63.1 GRBAS[3]

GRBAS is an acronym for five dimensions of voice quality referred to as 'Grade', 'Roughness', 'Breathiness', 'Asthenia' and 'Strain'. Speech and language therapists score their patients by giving a numerical value, i.e. an integer in the range 0–3, to each of these five dimensions of GRBAS.

BOX 63.2 VoiSS: Voice Symptom Scale[4]

VoiSS is suitable for general adult dysphonia populations.
Each item is scored 0–4 on the frequency response:
0 = never, 1 = occasionally, 2 = some of the time, 3 = most of the time, 4 = always

The **total VoiSS score (max = 120)** indicates the level of general voice pathology.

The **subscales** are completed by summation of items as follows:

Impairment: 1, 2, 4, 5, 6, 8, 9, 14, 16, 17, 20, 23, 24, 25, 27 (max = 60)

Emotional: 10, 13, 15, 18, 21, 28, 29, 30 (max = 32)

Physical: 3, 7, 11, 12, 19, 22, 26 (max = 28)

BOX 63.3 VHI-10 – Voice Handicap Index[5]

These are statements that many people have used to describe their voices and the effects of their voices on their lives. Ask the patient to circle the response that indicates how frequently they have the same experience:
0 = never, 1 = almost never, 2 = sometimes, 3 = almost always, 4 = always

1.	My voice makes it difficult for people to hear me.	0 1 2 3 4
2.	I run out of air when I talk.	0 1 2 3 4
3.	People have difficulty understanding me in a noisy room.	0 1 2 3 4
4.	The sound of my voice varies throughout the day.	0 1 2 3 4
5.	My family has difficulty hearing me when I call them.	0 1 2 3 4
6.	I use the phone less often than I would like to.	0 1 2 3 4
7.	I'm tense when talking to others because of my voice.	0 1 2 3 4
8.	I tend to avoid groups of people because of my voice.	0 1 2 3 4
9.	People seem irritated with my voice.	0 1 2 3 4
10.	People ask, 'What's wrong with your voice?'	0 1 2 3 4
	Total score	

BOX 63.4 Reflux Symptom Index[6]

Ask the patient to rate the following items on a scale of 0–5. The composite of these scores should be 10 or below. If it is more than 10, you should consider an evaluation to check for 'silent gastro-oesophageal reflux disease' or laryngopharyngeal reflux.
Within the past month, how did the following affect you?
0 = No problem → 5 = Severe problem

1.	Hoarseness or a problem with your voice	0 1 2 3 4 5
2.	Clearing your throat	0 1 2 3 4 5
3.	Excess throat mucous or postnasal drip	0 1 2 3 4 5
4.	Difficulty swallowing food, liquids or pills	0 1 2 3 4 5
5.	Coughing after you ate or after lying down	0 1 2 3 4 5
6.	Breathing difficulties or choking episodes	0 1 2 3 4 5
7.	Troublesome or annoying cough	0 1 2 3 4 5
8.	Sensations of something sticking in your throat	0 1 2 3 4 5
9.	Heartburn/chest pain/indigestion/stomach acid coming up	0 1 2 3 4 5

extraoesophageal (laryngopharyngeal) reflux. There are four main causes of voice disorders:

- inflammatory
- structural or neoplastic
- neuromuscular
- muscle tension imbalance.

Often, patients will have more than one condition contributing to their voice disorder. For example, a patient with vocal fold nodules may well have a degree of muscle tension imbalance and extraoesophageal reflux.

In assessing singers and other professional voice users, an understanding of their occupational and voice requirements is essential.[7–10]

In summary, it is important to determine:

- the nature and chronology of the voice problem
- exacerbating and relieving factors
- lifestyle, dietary and hydration issues[11]
- contributing medical conditions or the effects of their treatment
- the patient's voice use and requirements
- the impact on their quality of life, social and psychological well-being
- their expectations for outcome of the consultation and treatment.

Patients' complaints are most frequently related to:

- changes in voice quality (hoarseness, roughness and breathiness)
- a pitch that is increased or decreased which is not appropriate for their age and sex
- an inability to control their voice as required (pitch breaks, voice cutting out)
- an inability to raise the voice or make the voice heard in a noisy environment (reduced loudness)
- an increased effort and/or reduced stamina of the voice or one that tires with use
- difficulties or restrictions in the use of their voice at different times of the day or related to specific daily, social or work-related tasks
- a reduced ability to communicate effectively
- difficulty in singing
- throat-related symptoms (soreness, discomfort, aching, dryness, mucus), particularly related to voice use
- the consequent emotional, psychological effects caused by the above.

Many of the patient self-report questionnaires that have been developed to measure the impact of the voice problem on the quality of life are concerned with these areas of voice complaint.

Good examples of checklists for taking a detailed history in patients with voice disorders can be found in Mathieson[12] and Colton and Casper.[13]

General examination

The examination of a patient with a voice disorder should start with a general examination of the patient, as with any ENT disorder. Special attention should be given to the ears, nose and throat; for instance, the voice problem might be related to a blocked nose or sinus problems and can affect resonance and quality of the voice, as may be the case in professional voice users, or hearing loss causing the patient to strain their voice as they have to speak loudly to hear themselves.[14] The neck should be inspected for any scar that may indicate previous surgery or trauma, or neck masses, which will need a different sequence of investigations. A full neurological assessment might be necessary to assess the cranial nerve function or any signs of central neurological disease. The larynx is best examined with a videolaryngostroboscope, but this equipment may not be available at every centre.

VIDEOLARYNGOSTROBOSCOPY

Visual inspection of the larynx is mandatory for diagnosis or exclusion of laryngeal disease. This is usually performed in the clinic, but occasionally a diagnostic microlaryngoscopy needs to be performed when this cannot be tolerated in the outpatient setting or when the diagnosis is still uncertain (e.g. in some cases of chronic laryngitis).

The simplest method of examining the larynx and vocal folds is with a mirror.[7] Although excellent views can be obtained by an experienced examiner, the images are relatively small, of brief duration and frequently the anterior glottic region is not well visualized. In addition, the mucosal wave cannot be seen due to the relative speed of vibration of the vocal folds (usually over 100 cycles per second) compared with the ability of the retina to process individual images (five images per second).[8] Superior views of the larynx can generally be obtained using flexible fibre-optic and videoscopic transnasal endoscopes or rigid telescopes inserted through the mouth. Either approach has its own advantages and drawbacks. The transnasal flexible videolaryngostroboscope is associated with less gag reflex compared to the transoral rigid videostroboscopy. However, the rigid telescope may give a slightly better picture quality, although the distal tip high definition flexible videolaryngostroboscope provides images almost as good as those obtained on rigid videostroboscopy.[15] Occasionally both modalities may be helpful.[16] The examination should be recorded for further review if necessary.

Using a stroboscope gives additional information about the vibratory pattern of the vocal fold mucosa[17] and improves the accuracy of diagnosis.[18] It has led to changes in diagnosis in approximately 30% of cases when compared to examination with continuous light alone. Several rating forms for assessing the laryngostroboscopic images have been described, but none has been shown to have good inter- or intrarater reliability.[19] Although they are not used regularly in clinical practice, they are useful in ensuring that a systematic evaluation of the images is performed. The important features are listed in **Table 63.1**.

TABLE 63.1 Key features in the interpretation of laryngostroboscopic images

Laryngostroboscopic evaluation		
Glottal closure pattern	Anterior or posterior gap	
	Hourglass or spindle-shaped	
	Irregular or regular	
	Closed phase	absent/reduced/normal/prolonged
Mucosal wave (right/left) in response to changes in pitch and loudness	Symmetry	of amplitude
		of phase
	Periodicity (regularity)	regular/variable/irregular
	Degree of change	absent/decreased/increased
Description of lesion	Colour	
	Shape	
	Multiple/single	
	Surface	
Vocal fold opening/closing pattern (right/left)	Range full/reduced	
	Normal/lag	
	Presence of spasm/tremor	
Supraglottic appearance	False cords medial constriction: right/left/both	
	Anteroposterior constriction (arytenoid–epiglottic approximation)	
	Prominence/lesion(s)	
Symmetry of arytenoids (vocal processes and apices/corniculate cartilages)	Sagittal/coronal/axial planes	

Further assessment

If the diagnosis is not clear from the initial assessment, the patient may undergo one of the following options.

- further in-depth assessment by a voice therapist:
  - to ascertain more background information including exploration of contributing psychological issues
  - to undertake a probe or trial therapy to deconstrict the larynx and assess response to a treatment regime
- a trial of vocal hygiene/lifestyle advice or medical treatment
- laryngeal electromyography
- objective voice measurements (see Chapter 62, Evaluation of the voice).
- 24-hour pH monitoring ± impedance testing or oesophagoscopy
- diagnostic microlaryngoscopy
- referral to another voice disorders team or professional for a second opinion, such as a clinical psychologist, specialist singing teacher (familiar with voice problems in singers), neurologist, respiratory physician, gastroenterologist or upper gastrointestinal surgeon.

TREATMENT OVERVIEW

Ideally, the patient should be assessed in a multiprofessional voice clinic by a laryngologist and voice therapist and a joint treatment plan should be formulated. Not all patients presenting with a voice disorder want treatment and some may be happy being given a diagnosis, an explanation of their voice problem and reassurance that there is no serious underling condition present. If treatment is required, it will usually consist of one or more of the following options, depending on the patient's symptoms, vocal requirements and clinical findings:

- vocal hygiene, lifestyle and dietary advice
- voice (speech) therapy
- specialist therapy, e.g. singing therapy, osteopathy
- medical treatment
- phonosurgery.

Vocal hygiene, lifestyle and dietary advice

It is likely that most patients with a voice disorder will benefit from advice on vocal hygiene, lifestyle and diet. Depending on the relevance to the patient, this may consist of a discussion or video presentation in either individual or group sessions. Additional material is usually given in patient information leaflets. The areas covered may include:

- an explanation of how the voice works
- the links between lifestyle, phonatory and non-phonatory vocal activities and stress on voice disorders

- the potentially traumatic effects to the vocal folds of 'vocally abusive behaviours', such as talking or singing too loudly, talking too fast, shouting, throat clearing and harsh coughing
- communicating effectively without raising or straining the voice, e.g. using a whistle in the school playground or using amplification devices where practical and conserving the voice where possible or in extreme situations discussing the possibility of changing jobs
- the importance of adequate hydration for vocal fold function, i.e. by drinking water and use of steam inhalations, and avoiding excessive amounts of drinks containing caffeine, i.e. coffee, tea and colas
- smoking cessation, reducing alcohol and social drug consumption (particularly spirits, cannabis and cocaine) and avoiding exposure to fumes, dust and dry air
- diet and reflux reduction, e.g. avoiding eating late at night, large or fatty meals.
- For more details on these subjects, see Chapter 65, The professional voice, and Chapter 66, Speech/voice therapy for voice disorders.

Voice therapy

Voice therapy is the mainstay of treatment for muscle tension dysphonia (MTD) and may be delivered as an individual course of therapy, usually for no longer than eight sessions, or in groups. Examples of the latter include groups for voice care, professional voice users and for presbylaryngis.

The aims of voice therapy sessions are:

- to help the patient find a better voice quality which is stable, reliable and less effortful to produce
- to make better use of vocal resonance and tonal quality
- to increase the flexibility of the voice by improving the pitch range and loudness without undue effort
- to increase the stamina of the voice.

Various techniques are used, including one or more of the following:

- vocal exercises with the aim of targeting and strengthening specific muscle groups and improving glottal closure and efficiency
- increasing awareness of and reducing excessive tension in the muscles around the larynx, neck and shoulders
- advice on posture and improving breathing during speech
- laryngeal massage
- general relaxation exercises and stress management
- psychological counselling
- remedial singing lessons.

Some techniques may need additional specialist input from clinical psychologists, singing teachers and osteopaths, for example. Ideally, these individuals should be part of the extended voice disorders team (see Chapter 65, The professional voice, and Chapter 66, Speech/voice therapy for voice disorders, for more details).

Medical treatment

Medical treatment mainly includes treatment for acid reflux and upper respiratory tract infections and allergies. It may also include recommendations to change medication for other medical conditions, such as asthma inhalers, diuretics and other antihypertensive medication. The National Center for Voice and Speech has an excellent website which lists medications that can potentially cause an effect on the voice (http://www.ncvs.org/rx.html).[20] Botulinum toxin injections into the laryngeal muscles may be used in cases of spasmodic dysphonia and arytenoid granuloma.

Phonosurgery, including medialization procedures

Phonosurgery refers to any surgery designed primarily for the maintenance, restoration or enhancement of the voice.[21] It encompasses the following:

- phonomicrolaryngosopy
- injection laryngoplasty
- laryngeal framework surgery
- recurrent laryngeal nerve reinnervation
- laryngeal pacing.

More information can be obtained from Chapter 67, Phonosurgery, Chapter 54, Neurological disease of the pharynx, and Chapter 71, Contemporary management of laryngotracheal trauma.

PHONOMICROLARYNGOSCOPY SURGERY

A phonomicrolaryngoscopy is the examination of the larynx usually under general anaesthesia to further establish a diagnosis, but more importantly to surgically treat a pathology with the aim of improving voice. This is done with a suitable sized rigid laryngoscope. A good view is obtained by use of a microscope but inspection of the larynx with a 0- and 30-degree telescope is recommended. The larynx should be palpated too using crocodile laryngeal forceps. A sulcus or small cyst might be revealed which otherwise would not have without close inspection and palpation. The range of interventions includes biopsy and removal of lesions, vocal cord injection and laser surgery.

INJECTION LARYNGOPLASTY

This procedure aims to medialize an adductor vocal cord palsy where the cord is in a lateral position. There are different approaches and materials that can be used. The selection of injectable materials depends on the availability and the surgeon's experience. Most of the injectable materials are temporary and will only last an average of 6 months.[22] Injection laryngoplasty is discussed in greater detail in Chapter 78, Paralysis of the larynx, and Chapter 79, Outpatient laryngeal procedures.

LARYNGEAL FRAMEWORK SURGERY

Laryngeal framework surgery was first described by Isshiki in 1974.[23] It is defined as a procedure on the laryngeal cartilage to change the position or tension on the vocal cords in order to achieve the desired voice outcome. There are four different techniques, all with different purposes. These procedures should ideally be performed under local anaesthesia as originally described by Isshiki. This allows intra-operative auditory feedback to the surgeon and the patient and helps to assess the impact of the altered position of the vocal cords on the voice. Not every patient can tolerate a procedure under a local anaesthesia, however, and some patients may need general anaesthesia, but they will have the disadvantage of not knowing what their voice is going to sound like when they wake up! Further details on laryngeal framework surgery can be found in Chapter 78, Paralysis of the larynx.

RECURRENT LARYNGEAL NERVE REINNERVATION

The paralyzed vocal cord can be reinnervated to restore its function. The two techniques used are non-selective reinnervation and selective reinnervation.

Non-selective reinnervation

Non-selective reinnervation is indicated in hoarseness due to unilateral adductor vocal cord paralysis. It is performed under general anaesthesia via an ipsilateral neck incision at the level of the cricoid cartilage. The ansa cervicalis and the recurrent laryngeal nerve are identified and anastomosed using a 9/0 nylon suture.[24]

Selective reinnervation

Selective reinnervation is indicated in stridor due to bilateral abductor vocal cord paralysis.[25] It is performed under general anaesthesia via an extended anterior neck skin incision at the level of the cricoid cartilage. This is a more complex procedure that involves identification of several nerves for anastomosis. The C3 root of the phrenic nerve is identified on one side and anastomosed with a cable graft harvested from the great auricalar nerve in a Y-shape which is then inserted into both posterior cricoarytenoid muscles. The next step involves identification of the descending branch of the ansa hypoglossi and the recurrent laryngeal nerve on both sides of the neck and anastomoses carried out between these nerves bilaterally.

LARYNGEAL PACING

This technique is still being evaluated in clinical trials.[26] It involves inserting an electrode into each posterior cricoarytenoid muscle which then causes automatic abduction and adduction movement of the vocal cords. The electrode is connected to an external pacing device that is surgically fixed under the skin on the chest wall, in a similar way to a cardiac pacemaker.

SPECIFIC VOICE DISORDERS

The most common voice disorders seen in secondary practice in a voice clinic are:

- MTD
- laryngitis/MTD secondary to poor vocal hygiene, dietary and lifestyle issues
- extraoesophageal reflux (laryngopharyngeal reflux)
- vocal fold nodules
- vocal fold polyps
- vocal fold cysts
- vocal fold palsy and paresis
- arytenoid granulomas.

Less frequently seen conditions include:

- sulci and mucosal bridges
- spasmodic dysphonia
- papillomatosis
- microvascular lesions
- laryngeal trauma, including post-surgical causes
- other neuromuscular causes
- hyperkeratosis, dysplasia and carcinoma
- endocrine causes
- amyloid
- other laryngeal tumours.

Inflammatory disorders

OVERVIEW

Inflammation of the larynx can be broadly classified into infective and non-infective causes. Sometimes the aetiological factors are easily identified in the history (e.g. hoarseness associated with an upper respiratory tract infection). In many other cases the cause may be less clear (e.g. in cases of extraoesophageal reflux), may be multifactorial, may require empirical treatment or a biopsy and microbiological culture (e.g. in the case of tuberculosis) or may resolve spontaneously without a cause being identified. Patients often complain of:

- hoarseness
- huskiness
- reduced pitch
- loss of part of the range of the voice
- pitch instability
- an increased effort to speak
- vocal fatigue and pain or discomfort on speaking
- throat symptoms, such as globus sensation and irritation, dryness, throat clearing or chronic cough.

Laryngitis is simply a descriptive term indicating a variable degree of erythema, oedema, epithelial change which may include ulceration, leukoplakia and stiffness of the mucosa of the vocal fold. There is often an increased amount of thick mucus present, which may be white, grey, yellow or green in colour. There may be associated inflammation of the rest of the subglottic, supraglottic and interarytenoid

regions of the larynx and the pharynx. In severe cases, there may be associated shortness of breath and stridor. The voice is usually hoarse (rough, strained, breathy or whispery), which may be due to impaired vocal fold vibration due to stiffness from the inflammatory process and/or secondary to muscle tension imbalance. This can result in the vocal folds being held splinted apart and therefore extra effort being required to induce vocal fold vibration causing perilaryngeal pain or discomfort.

Accurate diagnosis may require a diagnostic microlaryngoscopy with biopsy. Treatment consists of reduced voice use and abuse, voice rest, vocal hygiene, lifestyle and dietary advice, and appropriate medical or surgical treatment.

SPECIFIC INFLAMMATORY CONDITIONS

Arytenoid granuloma

Arytenoid granulomas are benign inflammatory lesions that arise from the medial surface of the arytenoid cartilages, and in particular the vocal processes. Other terms for them include:

- contact ulcer or granuloma
- vocal process granuloma
- intubation granuloma
- contact pachydermia
- peptic granuloma.

These consist of a proliferation of granulation tissue with epithelial hyperplasia. They result from injury to the thin mucoperichondrium over the vocal processes from mechanical trauma, either following intubation or from repeated high-velocity impact of the vocal processes against each other from throat clearing, coughing or talking in a habitually low-pitched, creaky, hyperfunctional manner.[27] Men tend to develop granulomas secondary to hyperfunction, while women develop them more commonly as a result of intubation. In addition, extraoesophageal reflux is recognized as an important aetiological factor either contributing to the symptoms leading to the mechanical trauma or preventing healing of the damaged mucosa.[28]

Patients present with a change in the voice and/or vocal fatigue, a constant tickling sensation, discomfort or pain localized to the posterosuperior aspect of the larynx which is worse on phonation, coughing and throat clearing and can radiate to the ear. In addition, there may be symptoms associated with extraoesophageal reflux, including choking episodes and, in severe cases, stridor. These symptoms may come on insidiously, after intubation, an infection or a period of stress. They may be unilateral or bilateral and range from a nodular, diffuse thickening over the vocal process to large pedunculated, exophytic masses obscuring the posterior glottis (**Figure 63.1**).

The main treatment principles include reducing the effects of laryngeal irritants, i.e. stopping smoking, improving vocal hygiene, treating any respiratory tract infections, allergies and extraoesophageal reflux. Voice therapy, in terms of raising awareness of and reducing hyperfunctional and vocally abusive behaviour and psychological counselling where necessary, is also of use.[29] Surgery does not usually cure arytenoid granulomas when used in isolation as there is a high rate of recurrence. It is useful in confirming the diagnosis histologically, excluding a carcinoma and in debulking large lesions.[30] Laser vaporization after biopsy reduces the amount of bleeding but it is important to avoid thermal damage to the underlying cartilage.[28] There is no good evidence in support of the use of antibiotics or steroids in general. Botulinum toxin injections into the thyroarytenoid muscle can be useful as an adjunct treatment in resistant cases as this helps reduce the impact of vocal processes against each other, allowing the epithelium to heal.[31, 32]

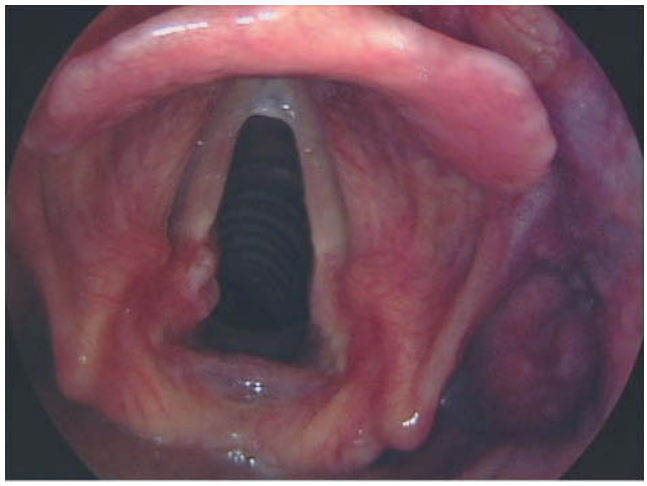

Figure 63.1 Arytenoid granuloma.

Structural or neoplastic lesions

OVERVIEW

Structural abnormalities can result from neoplasms which may be benign or malignant, or trauma to the laryngeal skeleton or soft tissues. Tumours of the larynx and laryngeal skeletal trauma are dealt with elsewhere in the text (see Chapter 14, Tumours of the larynx, and Chapter 71, Contemporary management of laryngotracheal trauma). This chapter will be confined to discussing the more common benign lesions resulting in referral to secondary care clinics and which involve the superficial layers of the vocal folds.

When a patient is observed to have a nodular swelling (i.e. a localized swelling on the membranous portion of one or both the vocal folds), it is important to consider the differential diagnosis in **Table 63.2**. Accurate diagnosis can be challenging and depends on a detailed history, the use of stroboscopy and, to some extent, objective measures.[33] Even then, a working diagnosis should be made and a decision needs to be made as to whether to try an empirical trial of therapy or proceed to a diagnostic microlaryngoscopy. A conservative approach is to reserve a 'microlaryngoscopy and proceed' for 'failed therapy' cases after appropriate informed consent.

TABLE 63.2 Differential diagnosis of a nodular lesion

Grey, white or translucent lesions	Haemorrhagic lesions	Yellowish lesions
True vocal nodules 'Physiological nodules' Prenodular swellings Pseudocyst Polyp Mucus retention cyst ± contact lesion Epidermoid cyst ± contact lesion Localized oedema of the vocal fold: • Reinke's oedema • Lower lip of a sulcus • Associated with a vascular abnormality, e.g. ectasia	Haemorrhagic polyp Ectasia Papilloma Carcinoma Arytenoid granuloma	Rheumatoid nodule Epidermoid cyst`

SPECIFIC STRUCTURAL OR NODULAR LESIONS

Vocal fold polyps

A true vocal polyp is a benign swelling of greater than 3 mm that arises from the free edge of the vocal fold (**Figure 63.2**).[34] It is usually solitary, but can occasionally affect both vocal cords. It is claimed that polyps are the most common structural abnormality that cause hoarseness and they affect men more than women. They are most frequently seen in smokers and between the ages of 30 and 50 years.

In many cases the exact cause of polyp formation is not known, but most authors agree that phonotrauma is an important aetiological factor. Some are heralded by a sudden onset of hoarseness or loss of voice after yelling or shouting, particularly if the vocal folds are inflamed from acute infective laryngitis or extraoesophageal reflux. A large proportion of patients with vocal cord polyps are also smokers. Cigarette smoking can cause injury to the vocal cord leading to hyaline degeneration in polyps.[35] There appears to be disruption to the vascular basement membrane, capillary proliferation, thrombosis, minute haemorrhage and fibrin exudation.[36] Although some polyps have a haemorrhagic appearance, others are more gelatinous and grey. Whether these gelatinous polyps have a different pathogenesis is not known.[34, 37]

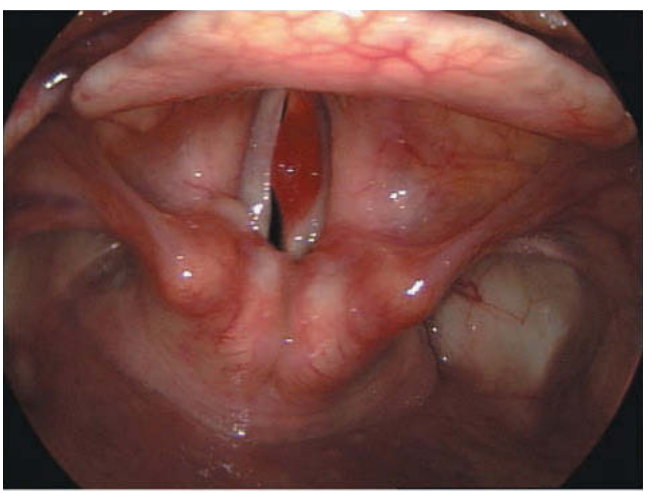

Figure 63.2 Vocal fold polyp.

Occasionally, a sulcus, mucosal bridge or intracordal cyst is found immediately opposite on the other vocal fold.[38, 39] It is hypothesized that in these cases the resulting disordered vibration and stiffness of the vocal fold make it more likely to damage the other vocal cord causing localized trauma and polyp formation.

Alteration in voice quality and voice complaints will depend on the effect of the mass of the polyp (and any other associated lesion) on vocal fold vibration, its effect on vocal fold closure and the secondary compensatory changes, i.e. increased muscle tension. The patient may complain that the voice is hoarse, has lowered in pitch and cuts out in speech, that they have lost part of the range of the voice and that it is a strain to speak.[40] Very rarely, large polyps can cause difficulty in breathing and episodes of choking.

Polyps can shrink spontaneously or even be coughed up. Voice therapy may provide the patient with coping strategies, preventative advice and help ease symptoms, but is unlikely to result in resolution of the polyp.[41] Any concomitant inflammatory conditions should be treated. Most polyps need removal under a general anaesthetic and a variety of techniques to achieve this have been described. This might be by using laser or cold steel suspension microlaryngoscopic technique (see Chapter 67, Phonosurgery).[42, 43] The aim is to restore the smooth edge of the vocal cord to allow them to close fully and vibrate normally.

Vocal fold nodules

Vocal fold nodules are small bilateral swellings (less than 3 mm in diameter) that develop on the free edge of the vocal fold at approximately the midmembranous portion (**Figure 63.3**). In some cases, particularly in singers, they may be smaller, more pointed and white in colour, reflecting a more superficial response to trauma. They may be associated with microwebs at the anterior commissure in up to 23% of cases. They are of variable size and are characterized histologically by thickening of the epithelium with a variable degree of underlying inflammation.

The exact incidence and prevalence of nodules in the general population is not known, but in various population studies nodules have been shown to be the cause of

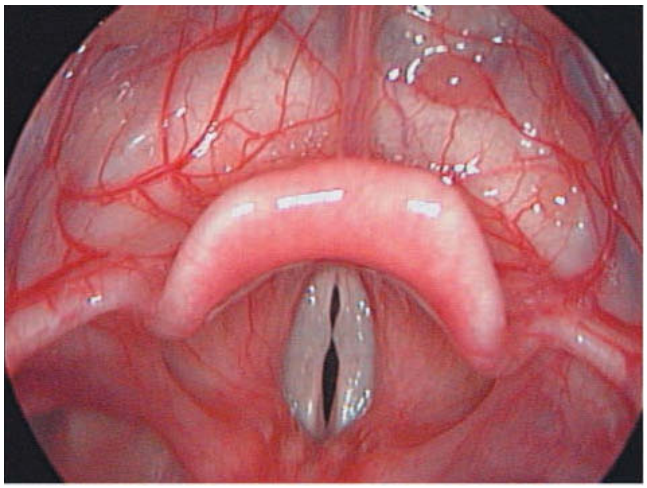

Figure 63.3 Vocal fold nodules.

persistent hoarseness in just under 25% of children and in 6% of adults with voice problems.[44] Higher percentages are found in teachers and singers with voice problems. In children, they are more common in boys than in girls, while in adults they are very much more commonly found in women, particularly under the age of 30.

The aetiology of vocal nodules is not known, but traditionally they are thought to be due to 'voice abuse' rather than overuse. Voice abuse is characterized by forced voice production due to strain in the neck and shoulder region producing a harsh quality to the voice.[45] It may be precipitated by talking for prolonged periods in a loud voice (often above background noise), repeated shouting and/or singing above one's natural range and occasionally repeated coughing and throat clearing. The vocal folds are thought to impact on each other in such a way that the repeated trauma of the midmembranous portions leads to localized swelling and epithelial thickening. Shearing forces may be important and a whiplash hypothesis has also been proposed.[46] Psychological factors, nasal, throat and chest infections, allergies and extraoesophageal reflux are increasingly being recognized as playing an important part in the aetiology of vocal nodules.[46–49] Nodules disappear spontaneously in boys with the relatively large growth of the larynx in puberty.[44] In girls, they may persist into early adulthood.

The voice quality is often husky and breathy, worsening with voice use and often associated with perilaryngeal discomfort or throat soreness on phonation. The voice may become a little deeper in pitch and associated with voice breaks, particularly at the higher end of the range of the voice. The vocal folds are usually hourglass in appearance with often only the nodules making contact at the midmembranous zone.

There is no good evidence on which to base the treatment of vocal fold nodules. Nodules may develop after the individual has been projecting and using their voice more than usual and often settle spontaneously once the demand on the voice returns to 'normal'. If nodules are not causing significant voice problems, they should be left alone. Aggravating factors, such as inadequate vocal fold lubrication, allergies, infections and extraoesophageal reflux, should be treated to reduce their irritant effects. In the UK, the mainstay of treatment for persistent vocal nodules is voice therapy with the aim of modification of lifestyle and vocal behaviour, providing information and guidance on voice care, producing the voice more effectively with less strain and coping strategies. Not infrequently the voice and voice function improves, but the nodules persist. Some argue that complete and rapid return of voice function is only possible if the nodules are excised. Others would reserve surgery for those who fail voice therapy and remain symptomatic. Most would agree that a significant number of nodules recur if surgery is performed without voice therapy either pre- or post-operatively.[50] If surgery is performed, the aim must be precise excision of the nodule alone with no exposure or damage to the underlying ligament.[43, 51]

Pseudocysts

The exact definition of a pseudocyst varies between authors. Some define it as a lesion that differs from cysts and polyps in that it has no cyst wall and is filled with serous fluid, having an appearance similar to that of a blister. Others have defined it as localized Reinke's oedema, which may indicate the presence of underlying paresis.[52] The exact aetiology is not known, but is probably phonotrauma. The initial management of a pseudocyst is by behavioural therapy. Surgical excision might be necessary in cases that did not resolved with speech therapy.[53]

Reinke's oedema

Reinke's oedema is a term used to describe the vocal folds when they become chronically and irreversibly swollen (**Figure 63.4**). Other terms for the condition include:

- polypoid vocal cord, polypoid degeneration or polypoid hypertrophy; cordal polyposis or polypoid corditis
- chronic oedema of vocal folds
- pseudomyxoma or pseudomyxomatous laryngitis
- smoker's larynx.

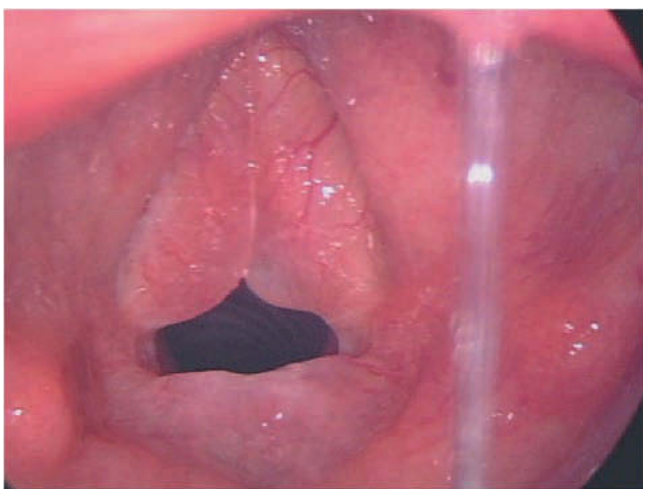

Figure 63.4 Grade 4 Reinke's oedema.

It occurs almost exclusively in moderate to heavy smokers, although the exact role of smoking in inducing these changes is not known.[54] Some studies have also suggested that voice strain and extraoesophageal reflux may also play a part in its development, although the importance of these other factors is not clear. Hypothyroidism may be found as a concomitant feature in some cases, but it is not thought to be an aetiological factor. The epithelium shows non-specific changes and the basement membrane layer is usually thickened. In Reinke's space, there are lakes of oedema, extravasated erythrocytes and thickening of the walls of the subepithelial vessels.

The true prevalence of Reinke's oedema is unknown. It is probably one of the most common conditions to affect the vocal folds in smokers and it is very likely that many people with this condition do not seek medical attention. A meta-analysis of 1538 cases showed that men and women are affected more or less equally, although the pitch-lowering effects on the voice are more conspicuous in women. Patients most commonly seek a medical opinion between the ages of 40 and 60 years of age.

Patients with even quite severe Reinke's oedema may have no complaints about their voice or problems with voice use. The most common symptoms are:

- deepening of the pitch of the voice with women often being mistaken for a man, particularly on the telephone
- gruffness of the voice
- effortful speaking
- an inability to raise the pitch of the voice
- choking episodes
- other symptoms associated with extraoesophageal reflux.

The diffuse lesions of the membranous part of the vocal fold are bilateral in 62–85% of cases, although they may be asymmetrical. Typically the vocal folds are grey or yellowish in colour with prominent superficial vessels. Alternatively, the oedematous folds may appear diffusely red when coexistent extraoesophageal reflux should be suspected. Leukoplakia is uncommon but may be due to hyperplasia, dysplasia or very rarely carcinoma in situ. In severe cases the vocal folds look like bags of fluid that flop up and down through the glottis with respiration. The severity of the swelling is best judged on deep inspiration and is frequently underestimated if an assessment is made solely on phonation as the oedematous tissue bunches up on the superior surface and into the ventricle. A severity grading system has been proposed and validated by Tan et al. (**Table 63.3**).[55] There may be a variable degree of associated increased muscle tension present.

The decision to treat a patient with Reinke's oedema depends on their symptoms, the severity of the oedema and the presence of leukoplakia. In most cases, conservative measures, such as reassurance, an explanation of their condition and vocal hygiene advice, including smoking cessation, should be tried initially. Hypothyroidism, upper airway infections and allergies and extraoesophageal reflux should be treated to reduce the throat symptoms associated with these conditions. The role of voice therapy is controversial but may be indicated if vocal hygiene issues and excessive MTD are prominent in a well-motivated patient. It certainly has a role in restoring voice function after surgical treatment.

TABLE 63.3 Grading of Reinke's oedema

Grade	Appearance
1	Marginal edge oedema
2	Obvious sessile swelling, thrown over vocalis muscle during phonation
3	Large bag-like swelling, filled with fluid
4	Partially obstructing lesion, medial borders in contact along most of length

Surgical treatment should be considered when:

- leukoplakia is present and a histological diagnosis is required
- gross Reinke's oedema is present causing choking episodes or airway compromise
- pitch elevation of the voice is the main requirement of treatment.

Other symptoms may not necessarily be helped by surgery and there is the potential for making patients worse by causing scarring or an irregular edge to the vocal fold. Patients must be aware that after surgery:

- friends and relatives may not recognize them by their voice
- the singing voice may be permanently altered
- speaking may be more effortful for up to 1 year (or occasionally permanently), particularly if excessive mucosa is removed due to stiffness from scarring and anterior web formation
- the voice seldom returns to 'normal', but is generally of better quality
- the Reinke's oedema is likely to return within 2 years if the patient continues to smoke.[56]

The principles of surgery for Reinke's oedema include:

- reducing the bulk of the mucosa (mass per unit length) of the vocal fold
- obtaining a straight mucosal edge, i.e. avoiding leaving small deposits of the myxoematous material behind
- avoiding damage to and exposure of the underlying ligament, thereby reducing the chances of scarring and web formation.

'Reduction glottoplasties' can be performed with phonosurgical instruments or one of the new generation of microspot lasers. KTP laser treatment of Reinke's oedema may be performed in the outpatient department under local anaesthesic via a channelled endoscope.[57] Care should be taken not to remove excised epithelium and not to overheat the vocal cord ligament as this may result in a permanent scar and hoarseness.[58] The myxoematous

material from the superficial lamina propria layer is aspirated, removed with forceps or vaporized and the epithelial edges apposed following excision of redundant mucosa as necessary. Good results from unilateral treatment have been reported with patients often electing not to have further surgery on the second side. Post-operative voice therapy may be required.

Endocrine causes

Hyperthyroidism has been associated with increased anxiety, hoarseness and tremor affecting the voice. The vocal folds have been reported as looking 'hypervascularized and hyperkinetic'. Hypothyroidism is associated with:

- hoarseness
- deepening of the pitch of the voice
- voice fatigue and weakness
- dryness of the throat
- slow and hesitant speech.

Small prevalence studies have not shown an increase in prevalence of biochemical hypothyroidism in patients with Reinke's oedema, but one uncontrolled study suggested that subclinical hypothyroidism may be more prevalent. Although the vocal folds are often described as being oedematous in hypothyroidism, there is little histological evidence to support myxoedematous infiltration of the vocal folds or muscles.

Abnormalities of endocrine function, in particular related to the thyroid and sex hormones, can have varied effects on the voice and voice function. Most have not been studied in great detail and are beyond the scope of this chapter. Of note are the effects of androgens and androgenic drugs, such as Danazol, which cause irreversible enlargement of the female larynx with the consequent effects of deepening of pitch. The fundamental frequency of the voice is lowered and the high tones lost at the menopause.[59]

Autoimmune diseases of the larynx

Laryngeal manifestions of autoimmune diseases are not uncommon and have been described previously. Examples are cricoarytenoid fixation, mucous inflammation, subglottic stenosis, vasculitis, laryngeal edema, vocal fold paralysis, infection, or vocal fold lesions such as vocal fold rheumatoid nodules and bamboo nodes.[60–63]

Bamboo nodes

Bamboo nodes are round pale yellowish lesions found in the mid third of the membranous vocal cord (**Figure 63.5**). It is because of their appearance that they are called bamboo nodes. These patients usually present with hoarseness. A blood test to exclude autoimmune diseases is mandatory if the patient is not already diagnosed with an autoimmune disease. Examples of autoimmune conditions associated with bamboo nodes are rheumatoid arthritis, systemic lupus erythromatous (SLE), Sjögren's syndrome, Hashimoto thyroiditis and systemic sclerosis. The blood test may reveal elevations in the sedimentation rate, rheumatoid factor, Sjögren's antibodies and antinuclear antibody titres, as well as hypergammaglobulinemia.

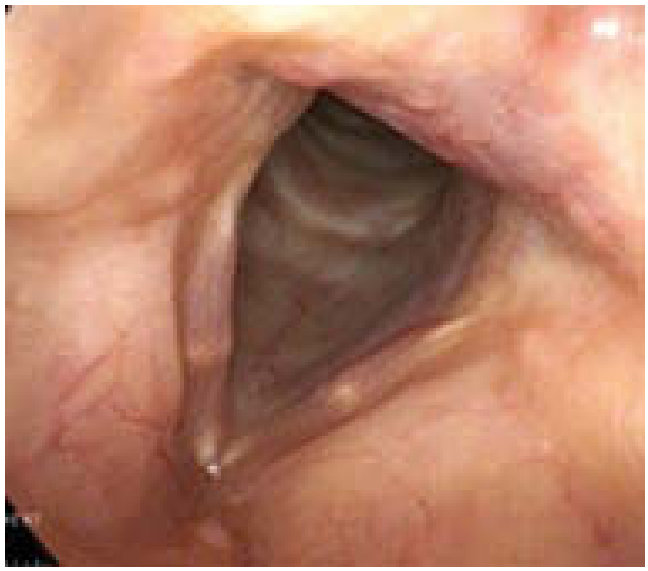

Figure 63.5 Bamboo nodes.

The diagnosis of a bamboo node is made from history and clinical examination. A videolaryngostroboscopy is essential to examine the vocal cords and the mucosal wave. This will give an indication of the effect of the node on the vocal cord vibration.

Conservative management is by speech therapy. A systemic steroid may be helpful but patients may not tolerate long-term treatment due to the side effects.

Steroid injection may be necessary in cases that have failed to respond to conservative management alone. This should not be given more than three times a year so as not to develop atrophy of the vocal cord.

Resistant cases may need phonosurgical excision of the nodes. Care should be taken not to damage the vocal ligament, which can lead to a permanent scar and hoarse voice. For this reason, this type of surgery should be done under a high microscopic magnification during a suspension microlaryngosocopy.[64, 65]

Cysts, sulci, mucosal bridges and vergeture

Cysts are found less frequently than polyps and nodules, and sulci and mucosal bridges even less so. There are two primary types of cyst: a mucus retention cyst and an epidermoid cyst. Both cause the voice to be constantly hoarse, which may worsen with use, with varying degrees of roughness and breathiness depending on the interference with vocal fold vibration and closure. Part of the vocal singing range may be affected, with pitch breaks or cutting out altogether.

A mucus retention cyst (**Figure 63.6**) is thought to arise from a blocked minor salivary gland, possibly secondary to phonotrauma or inflammation. It is lined by cuboidal or low columnar epithelium and can be associated with oedema and fibrosis in Reinke's space. It is usually unilateral and is found on the free edge of the vocal fold or

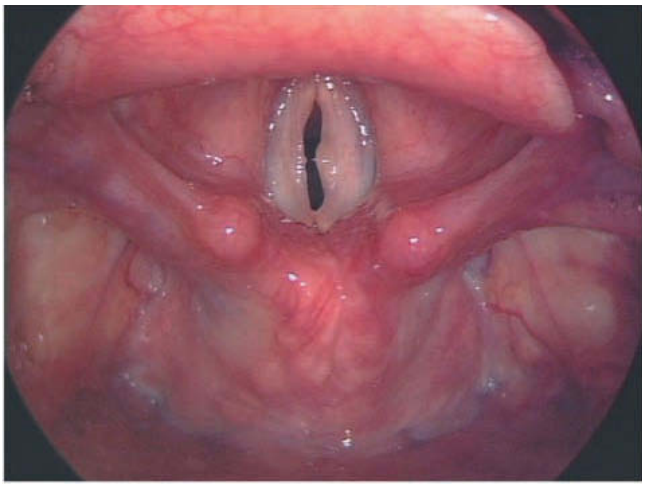

Figure 63.6 Mucus retention cyst.

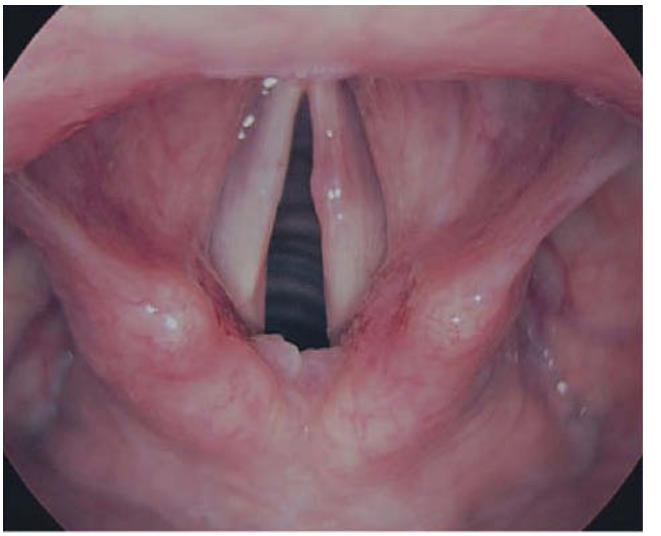

Figure 63.7 Epidermoid cyst.

can arise in the ventricular fold (false cord) (**Figure 63.6**). In the vocal fold they should be suspected in cases of asymmetrical nodular swellings (cyst plus contact nodule) and can be difficult to distinguish from polyps on laryngoscopy. Stroboscopy can help in the differential diagnosis, but frequently a definitive diagnosis can only be made on microlaryngoscopy and by performing a cordotomy.

Ventricular cysts need to be differentiated from other tumours (see Chapter 14, Tumours of the larynx). They can affect the voice by prolapsing on to the vocal fold interfering with vibration and causing secondary hyperfunction.

Epidermoid cysts (**Figure 63.7**) are lined by squamous epithelium and are filled with keratin and cholesterol debris. There is often an inflammatory exudate in the surrounding Reinke's space. It is unclear how these cysts develop, but various theories have been proposed including a metaplasia in a long-standing mucus retention cyst, microinclusion of epithelium from surface trauma or some defect in epithelialization during development (congenital or dysembryoplastic theory). They are thought to arise as a result of voice abuse and misuse. Large cysts cause a yellowish/white bulge within the vocal fold, but smaller, deeper cysts may only be suspected by the presence of localized absence or reduction in the mucosal wave on stroboscopy or abnormal blood vessels over the cyst or the appearance of unilateral or bilateral chronic laryngitis. The diagnosis may only be confirmed at microlaryngoscopy and cordotomy in these cases.

The term 'sulcus' has been used to describe different entities in the literature. Two entities can be distinguished: sulcus vocalis and mucosal bridge.

- A **sulcus vocalis** is best used to describe a localized invagination of the mucosa of varying depth[66] (**Figure 63.8**). These may be described as 'open cysts', which may describe their aetiology. The justification for this is that they are commonly found in association with epidermoid cysts and it would seem logical that trauma to the neck of a cyst would lead to it widening and discharging its contents.

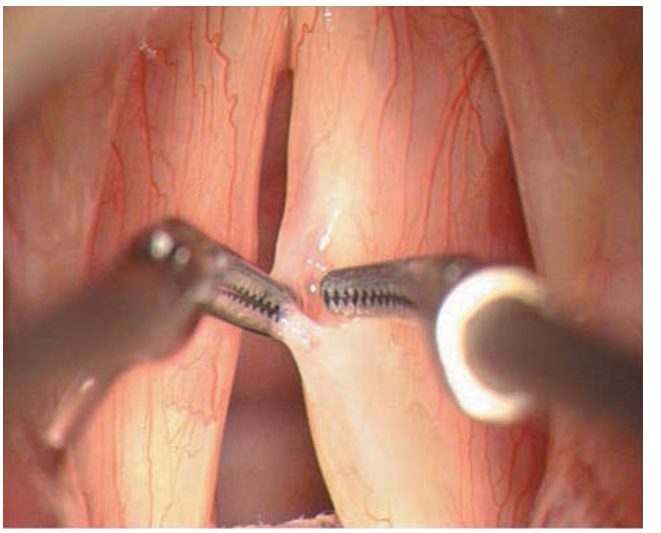

Figure 63.8 Sulcus vocalis. (With thanks to Romain Perouse.)

- Sulcus vocalis has been classified into three types:
  - **Type 1: Physiologic sulcus.** This is a superficial longitudinal depression of the epithelium not beyond the superficial lamina propria. The vocal ligament is not involved. Videolaryngostroboscopy may only show mild mucosal wave abnormally and the voice is not affected significantly. Treatment for this should be conservative with speech therapy and sometimes antireflux medication.
  - **Type 2a: Sulcus vergeture** (**Figure 63.9**). This is more extensive invagination extending into the vocal ligament with some loss of superficial lamina propria. Reinke's space exists superolaterally and inferomedially to the vergeture. They are thought to result from a congenital failure of development of Reinke's space as they are commonly apparent at puberty and can be familial. There is moderate mucosal abnormality on videolaryngostrobostoscopy and may have moderate dysphonia.

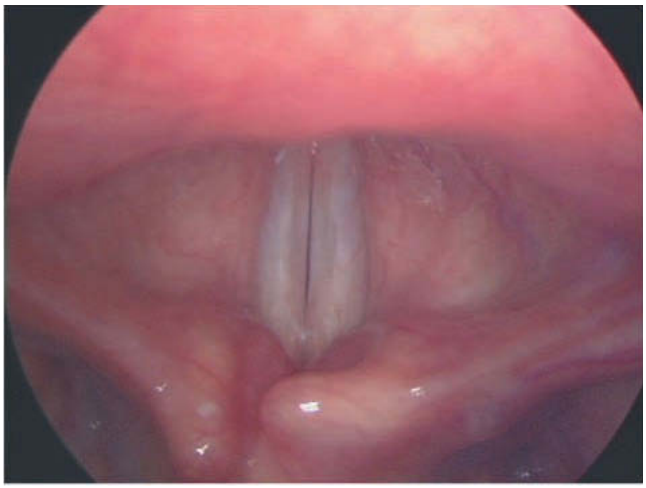

Figure 63.9 Sulcus vergeture.

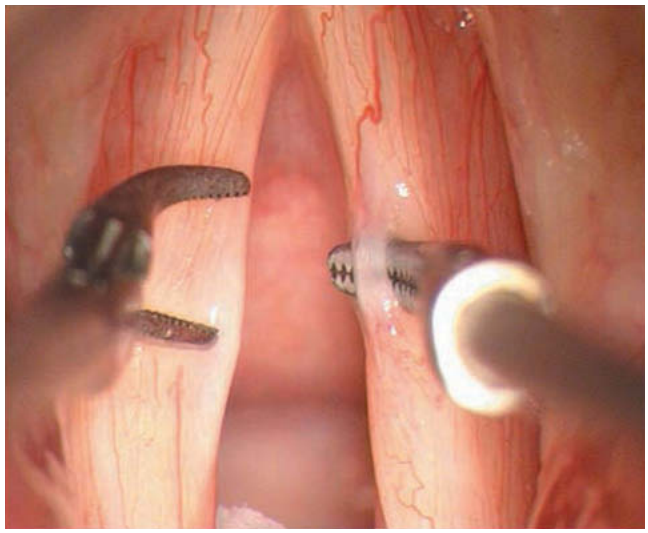

Figure 63.10 Mucosal bridge. (With thanks to Romain Perouse.)

- **Type 2b: Classic sulcus vocalis or a pouch type.** This is characterized by a focal pit that extends beyond the vocal ligament into the thyroarytenoid muscle. The is marked loss of superficial lamina propria. Video laryngostroboscopy shows significant mucosal wave abnormality with loss of vibratory pattern and patient may present with severe dysphonia.

- A **mucosal bridge** (**Figure 63.10**) may also be found in the presence of sulci and epidermoid cysts. This rare finding is thought to arise by the rupture through of the deep aspects of two sulci or cysts to form a tubed pedicle of mucosa.

Patients with sulcus vocalis and mucosal bridges present with variable degrees of dysphonia and roughness and breathiness, depending on the number of lesions, position and depth of the sulcus, the effect on glottal closure and degree of associated inflammation and MTD. Patients with sulcus vergeture often have a high-pitched monotone, weak (aesthenic), breathy and strained voice which is an effort to produce.

Patients with vocal fold cysts should be given a trial of voice therapy, particularly when symptoms are relatively mild. Many will require surgery but this must be done precisely, preserving the overlying mucosa as much as possible. It is important to avoid leaving part of the wall behind, which will result in a recurrence or cause localized scarring and poor voice results. This is more so for mucus retention cysts as dissection of the thin wall is more difficult. Post-operative voice therapy helps patients to restore vocal function and improvement may continue for up to 9 months. There may occasionally be problems with glottal closure following excision of large cysts and fat or collagen medialization may be of benefit. Ventricular fold cysts should be removed to confirm the diagnosis. There is the potential that they can cause airway obstruction if large or they become infected. Complete sharp dissection of the cyst with microlaryngoscopy instruments or with the laser is the treatment of choice.

The treatment of both types of sulci is difficult and the results variable. If surgical treatment is required for sulcus vocalis, careful dissection of the pocket off the ligament is required. The difficulty is in defining the plane between the base of the sulcus and the ligament and avoiding excessive resection of the mucosa and damage to the ligament.[67] Sulcus vergeture may be best treated by bilateral medialization procedures rather than attempted resection of the vergeture, which is technically extremely difficult.[68]

The ongoing challenge in the management of sulcus is that no single treatment modality is superior to others and no sufficient evidence for matching a given treatment to a given patient is yet available.[69]

Laryngeal hyperkeratosis

Laryngeal keratosis is an inflammatory disease of the epithelium of the vocal cords due to chronic hyperplasia and hyperkeratosis of the laryngeal mucosa with the resultant hyperkeratosis of the vocal cord epithelium. The aetiology is non-specific but it may have association with smoking, alcohol and reflux. The predominant symptom is hoarseness.[70]

The appearance is of white plaques, which can be confluent or patchy (**Figure 63.11**). Often the terminology is interchangeable with leukoplakia. *Leukoplakia* is a Greek word for a white plaque that cannot be simply scraped off. A histological diagnosis is mandatory to exclude neoplasia or dysplastic lesion. Laryngeal hyperkeratosis may appear easy to excise but laryngologists know that this condition is notorious for recurrence.

The management is by suspension microlaryngoscopy and surgical excision for histology. This condition may be precancerous, hence a biopsy is required. However, the treatment should be a conservative surgical approach to improve or maintain voice. Cold steel and laser therapy have been used but there is anecdotal evidence that an angiolytic laser such as the KTP laser offers longer-term cure.

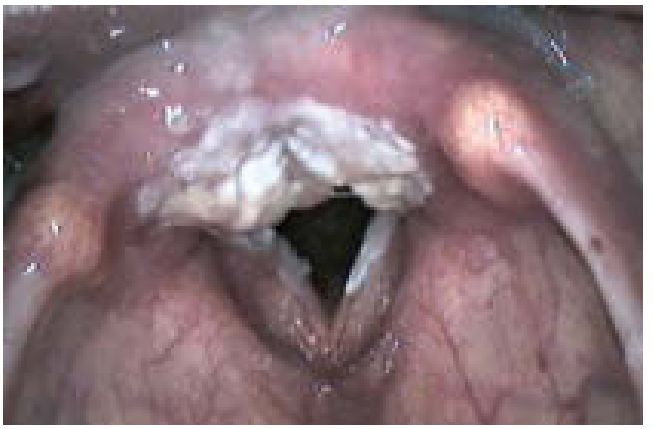

Figure 63.11 Laryngeal hyperkeratosis

Ackermann's tumour (verrucous carcinoma)

Ackermann's tumour is a slow-growing variant of squamous cell carcinoma that does not metastasize. It can cause a diagnostic and treatment challenge for both the histopathologist and the otolaryngologist. Macroscopically it may be hard to distinguish from hyperkeratosis. It has a typical exophytic appearance (**Figure 63.12**).

Although radical treatment such as laryngectomy is not necessary, a complete endoscopic excision is recommended to prevent recurrence. This tumour is less radiosensitive than others but extensive tumours may be treated with radiotherapy instead of radical surgery.

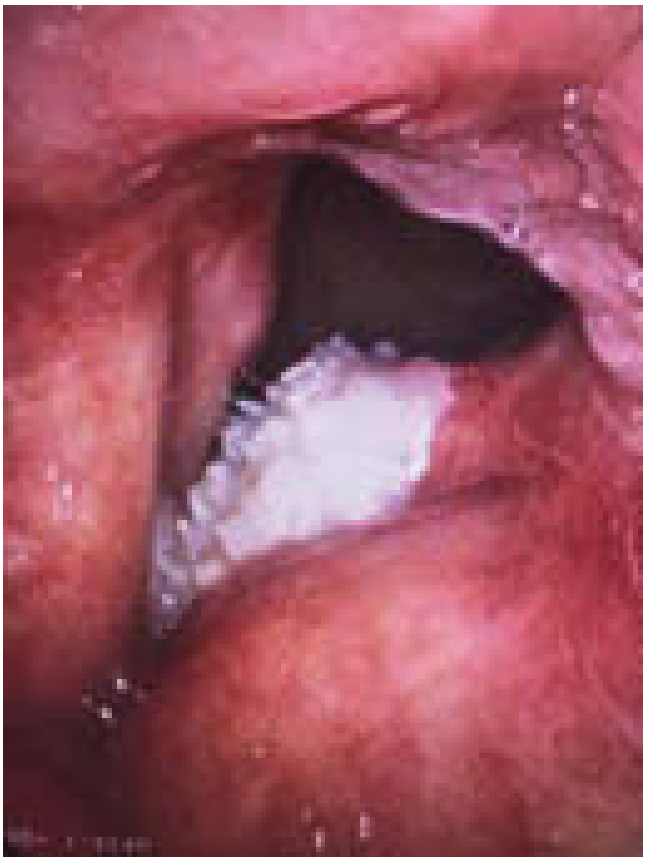

Figure 63.12 Ackermann's tumour (verrucous carcinoma).

Microvascular lesions

Microvascular lesions (varices or capillary ectasias) are collections of abnormally large and weakened vessels that are most commonly found (83%) on the superior or medial aspect of the midmembranous portion of the vocal folds (**Figure 63.13**). They are most frequently seen in professional vocalists (including singers) and are thought to arise secondary to repetitive trauma, hormonal variations or repeated inflammation. They may occasionally be incidental findings but can result in vocal fold haemorrhage, scarring and polyp formation. The lesions can interfere with the vibratory pattern of the vocal folds, causing a lack of clarity of the voice, vocal fatigue or sudden dysphonia associated with haemorrhage.

Voice and singing therapy, treatment of associated inflammation and occasional precise vaporization or point diathermy of the feeding vessel(s) may be required. Recurrences may still occur after treatment.[71]

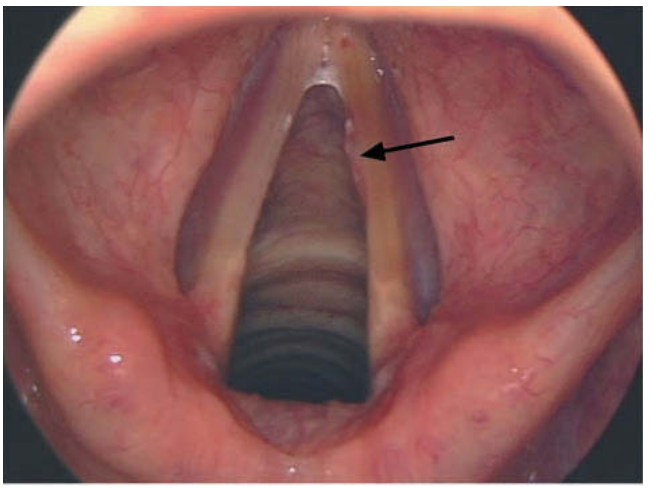

Figure 63.13 Microvascular lesions (arrow).

Neuromuscular causes

Neuromuscular causes are considered in detail in Chapter 54, Neurological disease of the pharynx. Apart from a vocal fold palsy, they are relatively uncommon. The prevalence of vocal fold paresis in dysphonic patients is unknown, but appears to be higher than previously thought if monopolar needle electrodes are used to detect the condition.[72] A palsy or paresis should be considered in any case where the complaint is of effortful phonation, throat discomfort or vocal fatigue with use or where the voice 'cracks'. Perceptually, the voice may sound breathy, unstable or higher in pitch. An obvious laryngeal paresis will show asymmetry of movement on abduction and adduction, i.e. it 'lags behind' the normal side. This asymmetry may only be apparent on prolonged observation using a fibre-optic endoscope and asking the patient to phonate and then sniff repeatedly. More subtle signs are an asymmetry of phase and amplitude of the mucosal wave and apparent bowing on the affected side on stroboscopy.

An effect on the voice may be the first sign of a more general neuromuscular disorder, such as Parkinson's disease, motor neurone disease, multiple sclerosis and myasthenia gravis. Neuromuscular disorders should always be considered in patients where the vocal folds look normal but the pattern does not fit with an MTD or fails to respond to treatment or the dysphonia worsens.

Spasmodic dysphonia is an uncommon and frequently overlooked condition. Traditionally it is classified as adductor, abductor, mixed and tremor and respiratory forms, although further subtypes have been described.[72–74] The adductor form is characterized by a strained/strangled quality to the voice, which cuts out at the onset of phonation, while the rare abductor type (approximately 15%) is characterized by breathy breaks following consonant sounds.[72, 75] Some patients present with a whispery (compensated voice) that is easier for them to use in conversation. Others have a mixed form that becomes more obvious during treatment, as the untreated form often worsens or is complicated by tremor. The spasmodic laryngeal activity can be seen by careful observation with a fibre-optic endoscope during speech.

The mainstay of symptomatic treatment remains botulinum toxin injection into specific intralaryngeal muscles, although the results are not always predictable and poorer for those with the abductor form and those with tremor.[72, 76–79] Improvements in outcome in the future may come with better targeting of the involved muscles. Other surgical treatments for adductor spasmodic dysphonia are now available. These are Isshiki thyroplasty type 2 using a titanium bridge implant to separate the anterior commissure by a few millimeters.[80, 81] Selective laryngeal adductor denervation–reinnervation surgery (SLAD–R),[82, 83] CO_2 laser thyroarytenoid myoneurectomy.[84, 85]

Muscle tension dysphonia or 'functional dysphonia'

OVERVIEW

Muscle tension imbalance causing MTD is one of the biggest causes or contributors to voice disorders. Although it is often a 'diagnosis of exclusion', i.e. the 'the vocal folds look and move normally', it is often present with inflammatory, structural and neurological conditions as laryngeal muscles try to overcome a deficiency in the voice-producing mechanism, such as poor respiratory function, impairment of normal vocal fold vibration or nasal blockage affecting resonance.[86] In addition, MTD can lead to trauma and structural changes in the vocal fold mucosa, for example in some cases of nodules. It is for the laryngologist and voice therapist to agree a treatment plan with the patient in these more complex cases.

MTD is therefore a group of conditions characterized by an imbalance of the synergist and antagonist muscles affecting the vocal fold position and tensioning relative to one another and also the position of the larynx relative to the rest of the vocal tract (**Figure 63.14**). Usually one or more sets of muscles is hyperfunctional, giving recognizable patterns of clinical presentation and laryngeal appearance.[87, 88] It is now thought that previously described hypofunctional states either are 'end stages' of hyperfunctional laryngeal activity or represent an underlying paresis.[89] The hypotheses are:

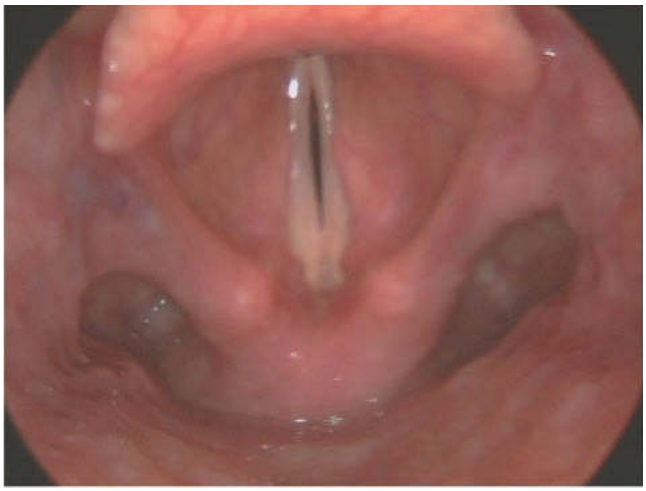

Figure 63.14 Muscle tension dysphonia. This is just one of the many patterns of muscle tension seen.

- that chronic imbalance of muscle pull, for example, of the cricothyroid muscle can lead to irreversible joint damage and ligament stretching giving a flaccid bowed appearance to the vocal folds
- that a viral neuropathic paresis has developed causing hypotrophy of the thyroarytenoid muscle and consequent poor glottal contact and secondary compensatory hyperfunction.[90] The evidence to support this comes from electromyographic studies.[72]

True hypofunctional cases do exist in neurological conditions such as myasthenia gravis, Parkinson's disease and motor neurone disease, but they are relatively uncommon.

There are multiple primary aetiologies of MTD[7, 29, 88] including:

- stress, anxiety and depression
- conversion disorders
- postural and breathing problems
- poor vocal hygiene
- talking in poor acoustic environments or above background noise for prolonged periods at work or socially
- exposure to excessive environmental dust, smoke or fumes.

The degree of dysphonia is variable, ranging from an intermittent problem related to a particular voice task (e.g. teaching) to severe and constant hoarseness. Other symptoms include:

- pitch of the voice may be too high or too low and reduced in range
- a sensation of tightness, constriction or lump in the throat
- effortful voice production
- discomfort on speaking or singing
- vocal fatigue.

The variability in the voice quality may be apparent during the consultation or with probe voice therapy. The laryngeal patterns on laryngoscopy have been classified into six main groups,[91] although some of these features may also be seen in the normal population.[92] Palpable increased tension and often tenderness in the suprahyoid, thyrohyoid and cricothyroid muscles may also be found, although these findings are not always consistent.[91, 93, 94]

Treatment, if required, consists of identifying precipitating causes and treating as appropriate, such as:

- vocal hygiene, dietary and lifestyle advice[29]
- voice therapy targeted at specific muscle groups[95]
- laryngeal manipulation[96]
- behavioural therapy[97]
- medical treatment, e.g. of extraoesophageal reflux.

SPECIFIC MUSCLE TENSION DYSPHONIAS

Puberphonia 'adolescent transitional voice disorder' or 'mutational falsetto'

Normally at puberty the voice drops by an octave in boys, but only three to four semitones in girls. In boys, the transition takes 18 months to 3 years and is usually completed by the age of 14. This voice change in puberty is accompanied by pitch instability and register breaks. The voice appears to be too high in pitch for the individual's age and sex and is often described as 'never broken'. The voice is often momentarily deeper on non-phonatory tasks, such as laughing or coughing and this is a key indicator of the condition. Even if it is recognized that the individual has 'two voices', i.e. higher and lower pitched, the latter is not perceived, as their voice is abnormal so consequently not used. The voice can tire and be effortful to produce on shouting or when projected. Occasionally, some patients experience pain and discomfort in the supralaryngeal region due to the elevated position of the larynx. There is often some associated psychological distress as the boys are frequently ridiculed and taunted because of their abnormal voice and inferred effeminacy.

As part of the normal pubertal changes, the total length of a boy's vocal cords increases by as much as 60%, reaching 17–23 mm in the bass voice with a relative increase in the ratio of the membranous and cartilaginous parts of the vocal cord. The thyroid cartilage virtually doubles in size and the dimensions of all other aspects of the laryngeal anatomy increase proportionally. The epiglottis changes from an omega shape to a more flattened shape. It also increases in size and elevates. The mucosal lining of the vocal cord becomes stronger and thicker. The cricothyroid muscle increases in bulk and strength to enable the thyroid cartilage to tilt forward for head or falsetto voice.

In puberphonia, the larynx tends to be held high in the neck, thereby shortening the vocal tract.[97] The cricoid cartilage is usually tilted backwards and the vocal folds remain too lax and limited in their ability to adjust to demands in change in tension and vibrational frequency. The vocal folds are stretched and thin with minimal mucosal waves. The cricothyroid remains excessively contracted. Acoustic analysis shows a speaking fundamental within the normal female range, intensity and harmonics-to-noise ratios within normal limits and a reduced contact quotient on electrolaryngography.

It is important to exclude organic conditions, such as endocrinological abnormalities, vergeture and scarring. Although most who present are keen to improve their voice, those who attend at the behest of family and friends and who are not concerned by their voice generally have a poor prognosis regarding resolution.

The treatment of choice is voice therapy,[97–99] although occasionally botulinum toxin injections into the cricothyroid muscles have been shown to be effective in resistant cases. Relaxation thyroplasty type 3 may be indicated in cases that failed speech therapy.[100]

Presbylaryngis

The ageing voice has certain characteristics.[101, 102] In males, the mean fundamental frequency tends to rise after the age of 50 and the voice is often perceived as high-pitched, thin and reedy in old age. In women, the mean fundamental frequency tends to decrease with age. Voice change may be related to the general fitness, voice use and previous training of the individual. The changes are related to ossification of the laryngeal skeleton, arthritic changes in the cricothyroid and cricoarytenoid joints, reduced muscle volume with a preferential loss of type I (slow contracting) muscle fibres, an increase in density of collagen deposition and decreased hyaluronic acid in the lamina propria, associated with a reduction in fibroblasts and atrophic changes in the epithelial layer. The net effect is stiffened, bowed, atrophic-looking vocal folds.[103] Other factors that will affect voice quality are laryngeal position, vocal tract atrophic changes and loss of lung capacity. Patients may just require an explanation of their voice problem and be happy with the exclusion of malignancy. If treatment is indicated, vocal care and voice therapy with the aim of building up the laryngeal musculature and improving vocal control are most usually offered.[104–106] Injection medialization procedures using fat, hydroxylapatite[107] or bilateral (modified) thyroplasties have been used with good effect, although the results with fat are less predictable.

BEST CLINICAL PRACTICE

- ✓ Best clinical practice is achieved by accurate clinical diagnosis with high-quality imaging techniques and having a patient-focused approach, taking into consideration their vocal requirements and concerns.
- ✓ A multiprofessional team approach allows cost-efficient, multidimensional assessment and targeted planning and delivery of treatment.

FUTURE RESEARCH

- There is a real need for multicentre studies to determine the best treatment options for almost all aspects of voice disorders.
- Fundamental questions need to be answered as to the role of inflammation, in particular extraoesophageal reflux and paresis in the aetiology of voice disorders.
- The management of sulcus vocalis and vocal cord scars remains a dilemma. Often the diagnosis is difficult in the outpatient setting and numerous cases are either misdiagnosed or missed completely as result. There is a need for a collaborative study on what is the best approach to diagnosis and management of this rare but not uncommon condition.

KEY POINTS

When assessing a patient, it is important to consider the following questions.

- Which one or more of the following four conditions is present?
  - inflammatory causes
  - structural or neoplastic causes
  - neuromuscular causes
  - muscle tension imbalance (dysphonia).
- Is there any suspicion of a malignant or premalignant condition?
- Which is/are the predominant condition(s) causing the symptoms related to the voice complaints? For example, the treatment of extraoesophageal reflux may be more effective in relieving the patient's symptoms in Reinke's oedema than surgical debulking.
- Which is or was the primary condition and which are secondary or compensatory? The symptoms and signs of a secondary MTD may mask the presence of an underlying paresis, for example.
- Will treating the 'easily treatable factors' improve the patient symptoms enough to either reverse structural laryngeal changes or improve the laryngeal biomechanics sufficiently for adequate functional voice production, i.e. the voice may not be perfect, but they can live with it?
- Could the potential complications of an intervention, particularly surgical treatment, create more problems than they help?

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CHAPTER 64

FUNCTIONAL DISORDERS OF THE VOICE

Paul Carding

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SEARCH STRATEGY

The information in this chapter can be explored more extensively by undertaking a Medline using the following keywords: functional dysphonia, non-organic dysphonia, muscle tension dysphonia, psychogenic dysphonia, vocal misuse and vocal strain.

INTRODUCTION

A functional voice disorder applies to an alteration of voice quality where there is no structural or neurological laryngeal pathology or where the dysphonia is disproportionate to the pathology detected. Nomenclature is problematic in this area and there are many synonymous and similar diagnostic labels in use, including (most commonly) 'functional dysphonia' and 'non-organic dysphonia'. These terms are generic and indicate characteristics of a syndrome rather than a specific diagnosis. Several key authors have defined several subcategories which more accurately reflect the underlying pathogenesis[1–4] and these will be discussed below. Functional disorders of the voice represent by far the commonest presentation to voice clinicians, accounting for at least 50 000 new cases per year in the UK.[5, 6] The impact of this condition is considerable: it is known to affect communication in all contexts, and is related to impaired personal and work relationships, low self-esteem and reduced quality of life.[6–8] In addition, people with functional dysphonia also suffer from increased levels of anxiety, depression and poor general health.[6, 9, 10]

It is also important to note that there is an overlap between 'organic' and 'functional' voice disorders and that they do not represent dichotomous disorders.[11] A number of benign vocal pathologies (e.g. vocal nodules, oedema of the lamina propria, contact granulations) are attributable to vocal hyperfunction, voice misuse and poor voice technique.[12, 13] Similarly, aberrant phonatory physiology viewed on endoscopic examination (e.g. bowing of the vocal folds, supraglottic constriction) may also be a consequence of vocal hyperfunction and poor technique.[12, 13]

THEORETICAL PERSPECTIVES

Most contemporary authors have accepted that functional disorders of the voice might usefully be divided into two different subcategories: 'muscle tension' dysphonia and 'psychogenic' dysphonia.

- **Muscle tension dysphonia (MTD)** is primarily the result of vocal misuse or poor vocal technique.[1, 2] In these cases, psychological factors are considered negligible or secondary. Furthermore, Morrison and Rammage[4] describe different types of MTD (based on endoscopic appearance) but with the understanding that they all arise from laryngeal muscle tension during phonation. They further suggest that psychological factors are important only insofar as they influence autonomic arousal.
- **Psychogenic dysphonia** is marked by loss of vocal control associated with 'disturbed psychological processes' (such as stressful life events at onset, anxiety or depression and actual conversion).[2] Some authors[1] consider psychogenic dysphonia as an example of classical (Freudian) conversion. Butcher et al[1] detail three types of psychogenic conversion dysphonia:
  - **type 1:** classical hysterical conversion dysphonia
  - **type 2:** cognitive behavioural conversion

- **type 3:** 'habituated conversion', in which the suppressed conflicts of a cognitive behavioural conversion have been largely resolved, but the vocal symptoms and musculoskeletal tension persist as a matter of habit.

It is a common clinical experience to see a mixed picture where some elements of both muscle tension and psychogenic dysphonia combine to make a function voice disorder which is complex to treat.[4] It is also recognized that the relative contribution of these factors may change for a patient over time.

PATHOGENESIS OF FUNCTIONAL DYSPHONIA

There are several ways to consider the pathogenesis of functional voice disorders.

One approach is to consider the 'voice capability' curve model. It is possible to conceive that the voice capabilities of the whole population would provide a Gaussian (normal) distribution (**Figure 64.1**).

Most speakers would fall into the blue area where their voice capabilities are average but perfectly adequate for their personal, occupational and social needs. A smaller number of the population are likely to have exceptional vocal capabilities (red area). These individuals are likely to have the following attributes:

- maximally flexible and responsive laryngeal structures – this will result in quasi-periodic vocal fold vibration with good amplitude and will produce an extensive dynamic range of both frequency and amplitude[14]
- patent oral, nasal, pharyngeal and laryngeal cavities and an ability to manipulate their relative dimensions to resonate the different harmonics of the sound source signal[34, 40, 43] – this will result in a voice which is appropriate 'timbre' and will facilitate good voice projection[15]
- excellent control of pulmonary function to 'excite' vocal fold vibration at the minimal phonation threshold and to maintain consistent transglottal airflow through different vocal tasks[16]

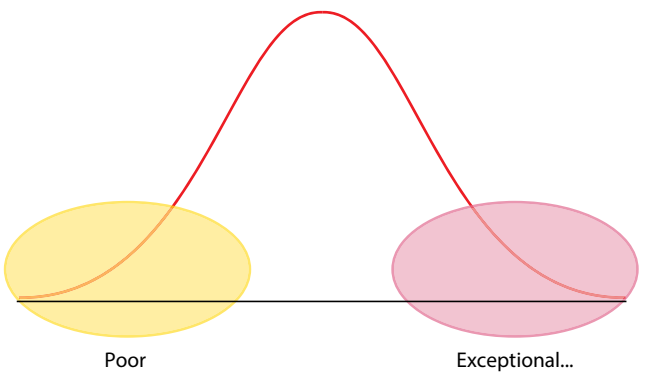

Figure 64.1 Voice capability.

- superior vocal technique (coordination of the first three attributes above) enabling smooth transition between different modalities of voicing and different vocal tasks without undue deterioration or fatigue[17]
- excellent paralinguistic features (speech rhythm, speed and vocal intonation) (see Chapter 60, Voice and speech production)
- superior auditory skills to constantly monitor vocal output, to maximize vocal effect and to detect any adverse voice quality changes.

Conversely, some speakers will have poor vocal capability and, hypothetically, these patients are more vulnerable to developing a functional or muscle tension disorder of the voice. These speakers are likely to have the following attributes:

- inflexible laryngeal structures with restricted vibratory amplitude and a limited dynamic range for both frequency and amplitude
- limited natural vocal resonance
- poor coordination of airflow for voice production
- limited awareness of vocal technique or ability to adapt vocalization depending on the task
- poor paralinguistic features
- limited auditory skills and auditory awareness of their own vocal characteristics.

It follows that people with limited vocal skills and capability are more likely to develop voice problems. This may be especially true if they experience a period of ill health, adverse life events or large vocal demands, for example. These additional factors are explored more fully below.

The more common approach to understanding the pathogenesis of functional voice disorders is to describe a constellation of predisposing, precipitating and perpetuating risk factors.[13, 18, 19] A recent review[19] stated that these multiple etiological factors can be categorized into three subgroups: vocal misuse and abuse, psychological and/or personality factors,[10, 20] and compensatory vocal habits for underlying laryngopharyngeal infection or disease. Similarly, other authors[13, 18] have identified four central tenants of MTD: gastro-oesophageal reflux, high personal stress levels, excessive voice use, and excessive vocal loudness demands. Clearly, not all of these factors need to be present in every case, and the relative contribution of each factor will vary between patients. Therefore, while the exact nomenclature may vary, it is common to conceive MTD schematically, as shown in **Figure 64.2**. It is important to note that previous authors have not discussed auditory skills in their explanatory models of functional dysphonia.

Deary[21] provides valuable further insight into these predisposing, precipitating and perpetuating factors and compares them to similar findings in other clinical areas of medically unexplained symptoms. He concludes that functional dysphonia appears to bear 'a striking resemblance to other medically unexplained conditions in terms of what

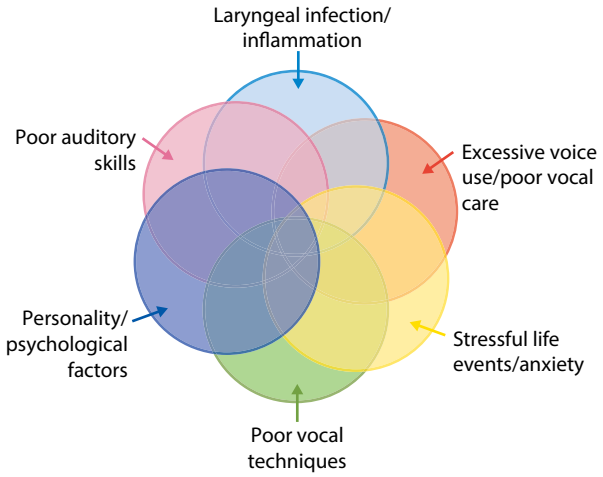

Figure 64.2 Predisposing, precipitating and perpetuating factors in functional dysphonia.

starts, triggers and maintains it'. Furthermore, he suggests a patient profile which is likely to increase the susceptibility for functional dysphonia.[21] This profile includes:

- a vocally demanding occupation[22]
- an abusive childhood[7]
- a 'distress-prone' and/or neurotic personality[23]
- a 'perfectionist' personality[24]
- a series of life events prior to onset[25]
- a history of fatigue.[24]

The literature would suggest that high vocal demand remains the most significant 'risk' factor for functional dysphonia. There are many studies that indicate the high prevalence of professional voice users among voice clinic attendees.[18, 26] While some authors remain entranced by the Freudian notion that the lack of voice has symbolic significance,[1–3] it is more likely that the voice is simply the vulnerable point (due to excessive demand) that breaks first in a person who is generally stressed and unwell.[21]

In conclusion, functional dysphonia is a diagnosis by exclusion (of pathology). However, it is a generic term that requires further investigation and analysis. A full understanding of the nature of an individual's functional voice disorder can only be determined by a detailed and comprehensive case history and interview. Appreciating the relative balance of the predisposing, precipitating and perpetuating factors for any one individual is paramount to successful treatment.

TREATMENT

There is strong evidence that voice therapy by a specialist speech and language therapist is a highly effective treatment for functional dysphonia. The objectives of voice therapy for this condition are twofold: to return the patient's voice to normal (or best possible voice within their anatomical and physiological capabilities) and to satisfy the patient's occupational, social and emotional vocal needs.[12, 27, 28] Voice therapy generally consists of a combination of indirect and direct therapy approaches. Direct therapy involves specific, targeted exercises to control and coordinate the various aspects of the vocal system.[28–34] Indirect voice therapy concentrates on helping the patient manage the contributory and maintaining aspects of the voice disorder and includes patient education, voice care advice, stress management and general relaxation.[28–34] **Table 64.1** lists typical direct and indirect voice therapy techniques for functional dysphonia.

A Cochrane review in 2009,[5] which reviewed articles up to 2007, stated that there was good evidence of the benefits of voice therapy for patients with functional dysphonia (six studies met their inclusion criteria; (total n = 163, controls = 141). Only randomly controlled studies that included patient-reported outcome measures (PROMs) were selected for detailed review. Three studies support a combination of direct and indirect voice therapy, and there is some evidence that indirect therapy alone is effective for particular patients.[5] A further review published in 2011[46] describes additional strong evidence for voice therapy intervention for functional dysphonia as well as an acknowledgment of the need to measure outcome from a multidimensional perspective. A number of recent treatment effectiveness studies have published details of voice therapy content.[47–52]

While traditional voice therapy has been shown to significantly improve the voice, there is limited evidence to date of any effect of this approach on the more general well-being of patients.[6] This has led many commentators in the field of functional dysphonia[1, 12, 27, 38, 41] to call for broader issues to be addressed in the treatment of these patients. Given the level of distress that some patients experience, professional psychological interventions may be necessary to augment existing treatment.[21] Roy suggests that, if the key predisposing, precipitating or perpetuating features of the functional dysphonia are not addressed, then relapse is a likely consequence.[41] Several recent studies[44, 45] report promising findings from CBT-enhanced voice therapy effectiveness studies. Treating the distress, along with the voice, could lead to more general and lasting improvement in patients. However, large longitudinal studies are required to examine these complex issues.

TABLE 64.1 Direct and Indirect voice therapy techniques

Direct	Indirect
Yawn–sigh method[31]	Vocal rest[32, 39]
Chewing technique[32, 42]	Patient education[32, 39]
Vocal function exercises[33]	Reassurance and counselling[42]
Airflow therapy[34]	Vocal hygiene programme[32, 38]
Resonance therapy[35]	Auditory training[31]
Deconstriction therapy[36, 37]	Elimination of voice abuse[31, 42]
Easy vocal onset techniques[36, 37]	Vocal diary[31]
Pitch variation and control[34, 39]	Avoidance of laryngeal irritants[39]
Confidential voice therapy[38, 42]	Hierarchy analysis[32]
Accent voice therapy[40]	Voice conservation[32, 39]
Voice skills therapy[17]	General relaxation[39]
Laryngeal manipulation[41, 42]	
CBT-enhanced voice therapy[44, 45]	

KEY POINTS

Functional dysphonia represents the most common presentation of functional disorders to voice clinicians

- There are several subcategories of Functional dysphonia including muscle tension dysphonia and psychogenic dysphonia.
- Functional dysphonia is not dichotomous from organic dysphonia (some untreated functional voice disorder may result in benign organic pathology)
- One way to understand the pathogenesis of functional voice disorder is to consider the voice capability curve model.
- There are a number of predisposing, precipitating and perpetuating factors in functional voice disorders.

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CHAPTER 65

THE PROFESSIONAL VOICE

Declan Costello and Meredydd Harries

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SEARCH STRATEGY

Data in this chapter may be updated by a PubMed search using the keywords: dysphonia, singer, actor, performer, professional voice user and voice clinic.

INTRODUCTION

What is the professional voice? A broad range of professions are reliant on their voices to conduct their work including teachers, telephonists, telesales workers, lawyers and many others. This chapter concentrates specifically on individuals who rely on their voices, speaking and singing, for performance at either a professional or an amateur level. For a clinician, it can be flattering to be asked to see a famous performer in the voice clinic but it is important to remember that the same standard of professional service is demanded for all patients, whether they are a primary school teacher or a top professional singer in a West End musical.

PARTICULAR PRESSURES AND DEMANDS ON PERFORMERS

Singers, actors and other performers work in an extremely competitive world. An inexperienced performer may feel considerable pressure to take on a role that is outside his or her range, or that places vocal demands beyond where they are comfortable. The hours of rehearsal are often extensive and it is not unusual for there to be up to eight performances in a week, but performers are reluctant to complain about such working conditions. Indeed, performers often continue to use their voices for long periods after they have developed vocal problems, which can compound their vocal pathology as a consequence. The reluctance to consult a laryngologist is exacerbated by a stigma about vocal ill health, in which the performer worries that they will not be given further work if it is perceived that they are 'fragile'.

The members of the voice clinic should be sensitive to all of these demands and the emotional stress that goes alongside them.

HISTORY

Vocal performers are often exquisitely sensitive about subtle changes in their voices and will be able to pinpoint very precisely the nature of their problem. The consultation should start with an open question allowing the patient to explain their difficulties.

The **style of singing** undertaken can have a profound effect on the ability of a performer to sustain their vocal instrument: singing in the musical theatre style, for example, has a tendency to be very vocally demanding, with a high 'closed quotient' (the vocal folds being closed for a large proportion of the vibratory cycle). The same can be said of many styles of rock and pop singing. In the popular music genre, there is the additional problem of the Lombard effect, i.e. the tendency to increase vocal

intensity in response to increased background noise. In the absence of any auditory feedback, singers tend to oversing and generate ever more strained patterns of laryngeal muscle usage.[1]

A change in **repertoire** can have a great impact: it is not unusual, for example, for singing students to be required to change their repertoire from one college term to the next. A change of repertoire requires a change in the set-up of the laryngeal musculature and can lead to vocal problems.

The extent of **vocal training** is an important factor. It is surprising how many young performers have relatively little training and are thrown into rehearsal and performance schedules without adequate preparation. This is particularly true for amateur and semi-professional performers.

Some performing roles require **specific vocal demands**. This might include foreign accents, shouting or other vocal effects. If these gestures are unfamiliar to the performer, or if they are to be sustained for a whole performance, they can lead to unhelpful muscle tension patterns and even vocal fold phonotrauma.

MAINTAINING VOCAL HEALTH

Most performers are aware of the importance of warming up their voices. Warm-up regimes vary from performer to performer, but the aim is to prepare the voice for the performance to follow. For many, this will involve humming exercises, sirening (a glissando sliding of the voice from low to high) and singing scales and arpeggios. These warm-ups should not (at least initially) be performed at full vocal intensity. The aim, as with an athlete warming up before a race, is to encourage blood flow to the muscles, and to encourage flexibility in the muscles and other structures of the vocal tract. The application of good 'vocal hygiene' is of paramount importance.

PSYCHOLOGICAL ISSUES AND PERFORMANCE ANXIETY

Psychological issues are often a major factor in the vocal problems of professional performers. Major life events such as relationship difficulties, bereavement and changes in circumstances can have a profound impact on the patient's psychological well-being, and their vocal problems may be a subtle manifestation of this sort of strain. Delicate and tactful questioning is required to elucidate these factors, without suggesting that the problems are 'all in the mind' of the patient.

Performance anxiety can become a major barrier for singers and actors. For some, the heightened autonomic arousal can act positively but, for others, it can be very destructive. Some performers will require specific counselling and psychotherapeutic interventions to overcome such barriers. Beta-blockers have been used by musicians and athletes to prevent tremor but they have no beneficial effects on the voice and their use should be avoided in vocal performers.[2]

LIFESTYLE ISSUES

Much of the performer's working lifestyle revolves around late nights, meals late in the evening, and much travelling. All of these can lead to fatigue and, particularly the late meals, can exacerbate any problems with laryngopharyngeal reflux.

Frequent flights will have their own effects: the ambient noise in aircraft means that it is often necessary to raise the voice to be heard; performers frequently report that air conditioning has a 'drying' effect on the larynx, so adequate hydration when flying is important; and the closed environment of the cabin allows for easy spread of viral upper respiratory tract infections.[3]

In addition to their performing and travelling activities, social lifestyle factors can exacerbate a performer's problems. Young performers in particular think little of socializing several nights each week. Noisy restaurants and clubs place considerable demands on the voice that can significantly hinder the performer's ability to perform to the best of their abilities.

THE VOICE CLINIC

A professional voice user would expect – indeed, would often demand – to be seen in a clinic with a full range of equipment for diagnosis, which should include a stroboscope. A detailed discussion of assessment of the larynx can be found in Chapter 61, Assessment and examination of the larynx.

It is important that the patient has confidence in the voice clinic they are attending. It is not unusual for laryngologists themselves to have experience of performing, and this allows for a conversation in which the patient feels that the clinician has an insight into the demands placed on them. The use of musical terminology relating to vocal registers and styles will put the patient at their ease and will help the clinician to understand the patient's current problems.

It is common for voice clinics to employ a singing teacher in addition to a laryngologist and a speech therapist. Some clinics also use a psychotherapist and/or a physical therapist.

Voice evaluation

It is often the case that the normal conversational spoken voice in a vocal professional will be unaffected. As discussed above, the vocal professional will more frequently present with subtle problems relating to a certain aspect of their performing voice. It may therefore be useful to ask the patient to demonstrate the particular vocal difficulties they are experiencing by performing part of a song or speech that they find particularly problematic. Detailed evaluation in terms of objective acoustic analysis

(e.g. jitter, shimmer, noise-to-harmonic ratio) is less frequently required.

Physical examination

Palpation of the neck will reveal any neck masses or lymphadenopathy. It will also highlight any muscular tension or tenderness.

Stroboscopic examination of the vocal folds is mandatory: it is only with the benefit of high-quality videostroboscopic equipment that one will gain sufficient detail of the mucosal surfaces of the vocal folds to be able to exclude subtle pathology. Fibre-optic and mirror examination of the larynx are no longer acceptable modes of examination in vocal professionals.

Stroboscopic examination can be performed either with a rigid endoscope (70 degree or 90 degree) or with a chip-tip (distal-chip) flexible endoscope. The details of stroboscopy are discussed in Chapter 61, Assessment and examination of the larynx, but it is worth bearing in mind the biomechanics of examination in each situation. Rigid endoscopy requires the patient's neck to be slightly extended, and for the tongue to be protruded. The endoscope can then be advanced over the tongue and the vocal folds can be examined. Needless to say, this is a very 'unphysiological' position in which to be phonating. In general, it is only possible to elicit an 'ee' vowel in this position. By contrast, with the chip-tip endoscope passed through the nose, the performer can sing and speak almost as normal. A wide variety of vocal gestures can be performed, including those specific gestures that are causing the performance problems. This is particularly helpful when muscle tension is believed to be a feature. On the other hand, the images achieved with the distal-chip flexible endoscopes are not quite as good as the rigid views. Different vocal problems may call for different examination techniques, or sometimes both.

Feedback

A crucial part of the consultation with a vocal professional is the explanation of the findings. It is imperative to take time to explain the laryngeal images, so the patient can understand (and engage with) the plan of management.

SURGERY ON THE VOCAL TRACT

Surgery on the vocal folds themselves is described in Chapter 67, Phonosurgery. One aspect that must not be overlooked is that surgery on any part of the vocal tract can have a large impact on the voice. Changing the resonance chamber of the pharynx (by, for example, performing a tonsillectomy) can result in a change in the patient's voice. This is true also of nasal surgery or adenoidectomy.

Performers requiring surgery of other sorts should outline their profession to the anaesthetist: if possible, surgery should be performed using a laryngeal mask airway so as to avoid any trauma to the vocal folds.

ACUTE ILLNESS

Performers live in dread of developing an upper respiratory tract infection at any time, but particularly during a run of performances. It is important to differentiate between an upper respiratory infection with or without laryngeal involvement. An upper respiratory infection can be managed conservatively with adequate hydration and steam inhalations. If there is laryngeal involvement, particularly hyperaemia of the vocal folds, then ideally the performance should be cancelled. In certain circumstances where the performance is a career make-or-break situation, steroids may have a role to play but the risk is that they could lead to a vocal fold haemorrhage. Aspirin is also associated with vocal fold haemorrhage via its action on the platelets and should be avoided at all times by the professional voice user.[4]

Cancelling a performance can have serious consequences, both financial and professional, and it is recommended that full records of the consultation and examination, including stroboscopic images, be documented for reference.

MANAGEMENT

It is self-evident that the management of the patient will be governed by the pathology (or lack of it) found in the examination. However, other factors will come into play, and a selection of scenarios may help to illustrate and expand on this.

Performing arts student

A 22-year-old student at a performing arts academy is having problems with her voice. She is a music theatre singer, and typically becomes hoarse after a few performances. When she rests her voice for a few days, her voice returns, but she runs into similar difficulties when she starts another run of shows. She usually has to sing in one show each day for a week at a time. Examination shows soft vocal fold nodules in the usual locations.

- In this situation, one must explain that vocal fold nodules will often resolve with speech and language therapy and with the assistance of a good singing teacher.

Consider the same student again. She is now 25 years old and is having similar difficulties to those she experienced 3 years previously. She has seen two laryngologists in recent years, and has had extensive speech therapy and voice coaching. Despite this, she is having the same problems of vocal fatigue and inability to complete a run of shows. In fact, she now becomes fatigued after just five performances.

- This is now a difficult situation. She appears to have instituted all the necessary changes, and is still not able to perform to the required standard. Of particular concern is that she is not, at the moment, being required to

perform as frequently as a full-time performing professional: if she were in a professional cast, she would be expected to perform up to twice per day for 5 or more days per week. The clinician should have a frank discussion with her about this, and consider either surgical excision of her nodules or a change in her performing regime/style.

Professional opera singer

A 27-year-old professional opera singer asks for an urgent consultation: he has a performance tonight, but was having difficulties during last night's performance, and his voice has not 'felt right' today. The performance tonight is the last one for several weeks. There is no problem with his speaking voice and there are no other features in the history of concern. Examination shows mildly oedematous vocal folds but no focal pathology, and no evidence of hyperaemia.

- Given that tonight's performance is his last for some time, and that there is no evidence of vocal fold haemorrhage or hypervascularity, it would probably be reasonable to consider a single dose of a corticosteroid to help to reduce some of the laryngeal inflammation. It would be important to review the patient in the days after the performance to ensure that the inflammation has settled.

Rock singer

A 26-year-old rock singer is in the middle of a tour of the UK. After last night's concert, he was markedly hoarse and he has requested an urgent laryngeal evaluation. He has a further 15 shows to perform in the next 3 weeks, and his management team accompany him to his consultation. They are extremely keen to avoid cancelling any shows. Stroboscopic examination shows haemorrhage of the left vocal fold, with blood tracking under the whole length of the mucosal surface.

- You are duty-bound to advise absolute voice rest and that the remaining shows are cancelled. Vocal fold haemorrhage of this type can be catastrophic for a performer, and it is imperative that the voice is rested to attempt to avoid the formation of scar tissue.

KEY POINTS

- Vocal performers should be considered as 'athletes', with very specific professional demands.
- A detailed history is required, focusing on the specific vocal difficulties and whether there is any variability in the symptoms.
- A multidisciplinary approach in a voice clinic is essential, using the expertise of a laryngologist, a speech therapist and a singing teacher/voice coach.
- In addition to a discussion about the difficulties with the performing voice, the history should cover other aspects such as social voice usage and nights out.
- Stroboscopy (either rigid or via a chip-tip endoscope) is mandatory in the vocal professional. Video archiving is imperative.

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CHAPTER 66

SPEECH AND LANGUAGE THERAPY FOR VOICE DISORDERS

Marianne E. Bos-Clark and Paul Carding

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SEARCH STRATEGY

Data in this chapter are based on searches of the Medline, CINAHL, PubMed and Cochrane Library databases using the keywords: dysphonia, voice disorder, voice therapy.

INTRODUCTION

'Voice therapy' is used to describe speech and language therapy for voice disorders. This intervention is provided by clinicians who are called speech and language therapists (SLTs) in the UK, speech and language pathologists in Australia and the USA, and logopedists across much of Europe.

Voice therapy, as provided by SLTs, is the therapeutic treatment of a voice disorder diagnosed by an ear, nose and throat (ENT) specialist doctor. This chapter discusses the principles of management of voice disorders, and provides an overview of voice therapy interventions and their evidence base.

Voice therapy captures a wide variety of activities and interventions, and the evidence base of therapeutic interventions continues to develop. While both adults and children present with voice problems and voice therapy is the treatment of choice for a number of voice disorders, focus in the literature has been on the voice therapy treatment of adults with functional dysphonia. Even within this diagnostic group, clinical practice is varied. Depending on the organization of services, voice therapy may be provided by a community-based SLT or voice specialist SLT within a multidisciplinary team. The SLT may choose to use a specific, well-described programme of intervention carried out over a set number of sessions, or prefer an eclectic approach based on individual needs.

SLTs delivering voice therapy will need postgraduate training, as specific voice therapy interventions, such as certificated programmes described below, are not included in undergraduate degree courses. SLTs will also need knowledge and skills of anatomy and physiology, vocal pathologies, instrumental and perceptual voice measures, advanced communication skills and competence and experience in a range of appropriate treatments. Some voice therapy interventions need intensive voice training (e.g. Voicecraft)[1] while others, such as vocal function exercises,[2] can be self-taught from a provided package. Some interventions are pathology-specific (e.g. Lee Silverman Voice Therapy for Parkinson's disease (LSVT®),[3] while others, such as Estill Voice Training,[4] are used to improve function in both the disordered and the healthy voice.

Voice therapy embraces principles from biomechanics of voice production and motor-learning principles,[5–7] as well as psychological interventions to facilitate voice change in people with voice disorders.[8–10] In the management of voice disorders, the SLT is guided by clinical guidelines, as summarized in **Boxes 66.1** and **66.2**.[11] The American Speech and Hearing Association's clinical practice guideline for management of hoarseness for clinicians managing dysphonia is also recommended.[12]

BOX 66.1 Summary of the Royal College of Speech and Language Therapists clinical guidelines for the assessment of clinical voice disorders[11]

ASSESSMENT

Each individual is to be examined by an ear, nose and throat (ENT) surgeon prior to or simultaneously with SLT intervention, ideally in a joint ENT/SLT clinic.

SLT voice assessment to include:

- perceptual assessment of vocal and respiratory behaviour
- good quality voice recording, to allow instrumental analysis of vocal parameters such as aerodynamics, pitch, intensity, resonance, vibratory cycle and vocal quality
- perceptions of the individual about their voice disorder, its symptoms and impact on their life
- palpation of the extrinsic laryngeal musculature
- consideration of differential diagnosis of the voice disorder.

BOX 66.2 Summary of the Royal College of Speech and Language Therapists clinical guidelines for the management of clinical voice disorders[11]

MANAGEMENT

Intervention to include explanation and discussion of:

- normal anatomy and physiology for voice production
- causal and maintaining factors to the voice disorder
- voice care and conservation that will include hydration, environmental factors, voice use and lifestyle.

As part of the goal for more effective and efficient voice production, direct voice therapy approaches may aim to:

- alter vocal fold adduction
- reduce supraglottic activity
- adjust articulatory tension
- modify pitch
- alter resonance
- alter respiratory patterns.

Additional indirect approaches, e.g. relaxation strategies and psychological counselling, will be used where psychological or social factors are contributing to the development or maintenance of a voice problem. Their application may involve other members of the multidisciplinary team such as a psychologist.

UNDERSTANDING THE NATURE OF THE PROBLEM

Successful voice therapy must be based on a clear understanding of the problem.[13, 14] Since a voice disorder's aetiology is multifactorial, assessment needs to be systematic, use objective and subjective measures, and consider the impact of certain variables on individual patients.[15] Assessment data and diagnosis provided by the ENT are a starting point for therapeutic involvement. By considering the multifactorial aspects of the voice disorder, SLTs gain an understanding of the individual's voice in the full context of their life. SLT assessment requirements are summarized in **Box 66.1**, and salient aspects are discussed below.

Phonatory physiology

Detailed laryngoscopic examination gives SLTs information about phonatory physiology. Laryngoscopic findings can link directly to a therapeutic goal; for example, a finding of 'poor glottic closure and lateral false fold constriction' would guide intervention to restore vocal efficiency by reducing laryngeal constriction and improving vocal fold approximation. SLTs with appropriate training and supervision undertake laryngoscopy to gain detailed information about vocal fold function prior to therapy and during intervention to provide feedback to the patient.[16, 17]

Perceptual assessment

SLTs describe the presenting features of the voice disorder by listening to and rating the patient's voice quality in conversational speech and a standard reading passage, such as 'The rainbow passage' or *Arthur the rat*. There are different systems with differing terminology to describe the voice. Some require specific training, such as Laver's Vocal Profile Analysis Scheme.[18] SLTs use the GRBAS scale[19] to rate overall severity or **G**rade of voice change, **R**oughness, **B**reathiness, **A**sthenia and **S**train, where 0 = normal/typical; 1 = mild change; 2 = moderate abnormality; 3 = severe abnormality. The CAPE-V[20] is a more recent adaptation of the GRBAS scale, where SLTs also rate pitch and loudness on a visual analogue scale. Perceptual assessment is used continuously in voice therapy as a way of monitoring progress.

Instrumental measures

SLTs analyze voice samples from maintained vowels and connected speech with acoustic analysis packages, Laryngograph®, or with software such as PRAAT (the Dutch word for 'talk').[21] Instrumental voice measures are used in assessment before and after intervention, and these can also be helpful in providing visual feedback during treatment. Voice applications that display pitch and loudness can be downloaded on mobile devices and can support patients of all ages to practise voice work between sessions.[22, 23]

Asking the patient

SLTs investigate the voice complaint by thorough consideration of the patient's perspective. By filling in a questionnaire such as the Vocal Handicap Index,[24] Voice Symptom Scale[25] or Vocal Performance Scale,[26] patients rate voice symptoms and their impact. SLTs use these scores as part of outcome measurement, and to identify specific items to discuss more fully with the patient. During a detailed case history,[27, 28] patients outline what they have noticed about their voice, including hoarseness, limited dynamic range, poor projection, discomfort, fatigue and voice loss. Specific occupational and social vocal demands are identified, as well as strategies patients may already be using successfully to improve or maintain voice. It is important to note the language used by patients to describe their

voice problem. This reflects their understanding of what is happening to their voice, their expectation of therapy and their readiness to change. A successful case history will provide the clinician with relevant patient-specific information, build rapport and establish the SLT as a credible, skilled and trustworthy professional.[28]

THERAPY GOALS

Ideally, SLTs working with voice are part of a multidisciplinary team and take part in a joint voice clinic[29] or an SLT-led voice clinic. Within the team, the SLT's focus is always functional rather than structural.[14] As the relative importance of specific aetiological factors for a given individual are identified, patient-specific goals and an individualized intervention plan are developed. Broadly speaking, the aims of voice therapy are:

- to restore voice to normal (e.g. in functional voice disorders, muscle tension dysphonias, psychogenic voice disorders)
- to maximize voice function given permanent limitations (e.g. in vocal fold palsy, scarring, papilloma, post-radiotherapy voice)
- to reduce handicap and distress associated with the voice disorder (e.g. amplification, counselling)
- to establish strategies and vocal habits promoting vocal health so voice improvement is maintained.

These aims divide up into treatment goals linked to specific outcome measures and smaller, patient-centred goals (**Table 66.1**).[14] SLTs can personalize these goals further if required.

Joint goal setting is crucial to the success of voice therapy. This ensures therapeutic goals are specific and directly relevant to the individual with the voice disorder, clarifies expectations of both the patient and the SLT, and establishes the patient as an active partner in therapy, with the SLT as facilitator. When voice work is more personally meaningful to patients and they experience improved vocal control, motivation and compliance improve, and voice change is likely to be quicker and maintained better.[5, 30]

GENERAL THERAPY DESIGN AND DELIVERY

Clinical guidelines relating to intervention of clinical voice disorders are summarized in **Box 66.2**. There are a number of considerations for therapy delivery and design.

Individual or group

Voice therapy is usually delivered one-to-one, so that sessions can be tailored to the presenting condition, preferred intervention approach and vocal skills relevant to the individual. There are, however, aspects of voice intervention, such as delivery of voice care advice, that can be standardized and delivered in groups. One advantage unique to group voice therapy is that participants motivate and derive support from each other.[31]

Therapy content

Research suggests that effective voice therapy consists of a combination of direct and indirect approaches, rather than direct or indirect intervention alone.[26, 32, 33] Direct voice therapy consists of specific, targeted exercises to control and coordinate various aspects of the vocal system.[34] Direct therapy tends to work on phonation through facilitative techniques, a set programme of treatment, or a combination of approaches. Indirect intervention does not work directly on vocal skills, but on environmental factors, lifestyle issues, and general contributory and maintaining factors to the voice disorder.[34] Typical examples include discussing voice care advice, making patients

TABLE 66.1 Example of patient-centred goal setting related to outcome measure, for patient 'A', a supply teacher and rugby coach with hyperfunctional dysphonia and globus pharyngeus

Therapy goal	Suggested outcome measure
Eliminate mild bilateral vocal fold inflammation	Laryngoscopy
Establish voice within vocal norms on perceptual and instrumental measures	Clinician voice quality rating (GRBAS* or CAPE-V**) Laryngograph® or acoustic assessment
Eliminate vocal tract discomfort and tiredness	Patient rating Questionnaire
Eliminate habitual throat clearing	Chart and patient rating
Achieve effortless phonation	Patient report Clinician rating
Develop vocal projection skills to match demands of teaching/coaching	dB measure Patient report of performance and/or questionnaire
Experience reduced stress associated with dysphonia	Patient report Questionnaire

* GRBAS: Grade, Roughness, Breathiness, Aesthenia and Strain.[19]
** CAPE-V: Consensus of Auditory Perceptual Evaluation – Voice.[20]

aware of unhelpful habits, such as throat clearing, and explaining how the voice works. The proportion of voice therapy spent in direct/indirect intervention varies. Two methodologically different studies found that direct intervention constituted one-third[35] or more than two-thirds[36] of therapy time.

Hierarchical structure

Regardless of the approach chosen, voice therapy consists of incremental steps or skills that patients develop sequentially.[37, 38] Awareness of the amount of muscle tension or habitual level of loudness comes before producing voice with less tension or loudness, for example. In terms of the stimuli used for training and practice, SLTs control the level of difficulty so the desired voice quality can be successfully attained by the patient in different tasks. This may start in voicing without tension or roughness of vocal note on a single vowel sound, progress to rote speech (counting, days of the week), to reading aloud, and conversational speech. Carry-over or generalization strategies are integral to therapy,[38] so the desired vocal behaviour is present in clinic, at home and finally in the most vocally challenging settings for the patient.

Learning principles

SLTs are mindful of how vocal tasks are demonstrated, learned and practised. Certain intervention programmes, such as Estill Voice Training[4] and Lessac-Madsen Resonant Voice Therapy (LMRVT),[39] combine exercise principles with motor-learning theory and feedback to develop and maintain new vocal behaviour. The SLT's role is to guide the patient's awareness, perception and experience of better and healthy phonation during a session. It is thought that this specific attention and experience, in combination with distributed, random practice in different environments produces better learning.[5, 7]

Length of therapy

Although the literature reports considerable variability in length of therapy,[40, 41] it is suggested that patients attend no fewer than four to eight sessions to allow the voice change to take effect.[30, 38] Many programmes of intervention take at least eight sessions (e.g. LMRVT and LSVT).[39, 41]

Prognostic indicators

There are many variables affecting therapeutic progress. The following patient features are indicators of successful voice therapy:

- agreement of active role
- a willingness to change
- realistic expectations
- compliance and commitment
- elimination of other medical problems that may limit progress or stop the patient attending.

SLT factors likely to result in successful therapy are:

- high level of knowledge and skills of voice and voice techniques
- advanced communication skills
- ability to demonstrate listening skills, empathy, compassion, counselling
- ability to motivate.[42, 43]

Length of time from ENT referral to SLT appointment and length of therapy programme affect patient dropout.[44]

VOICE THERAPY APPROACHES

Indirect intervention

There is a wide range of activities in voice therapy where the SLT supports the patient in managing the contributory and maintaining aspects of the voice disorder. This includes explanation, stress management and general relaxation.[14, 34] The following activities are included in indirect voice therapy:

- vocal rest programme
- patient education, explanation of the problem
- vocal hygiene programme
- elimination of habitual coughing, throat clearing
- reassurance
- counselling
- general relaxation.

Direct intervention: Facilitative techniques

A number of facilitative techniques used by SLTs, many of them well described by Boone,[45] have been used historically by voice clinicians to stimulate and improve phonation.[34] These include:

- yawn–sigh
- chewing
- pitch variation and control
- reduction of vocal loudness
- elimination of hard glottal attack
- specific laryngeal relaxation
- voice 'placing'
- pushing exercises for glottal incompetence
- confidential voice.

Facilitating techniques are part of symptomatic voice therapy, and are used to establish best voice for the patient and subsequently practised to stabilize improved voice production.[43] There is no unifying evidence base or underlying theoretical framework as they are a wide range of techniques. Though evidence of efficacy in treatment is largely based on case studies, a skilled SLT may find these techniques a useful adjunct to other approaches.

Direct intervention: Voice therapy programmes

ACCENT METHOD

The aim of this method, developed by Svend Smith, is to resolve the voice disorder by improving coordination between breathing, voicing, articulation, body movement and language for individuals.[46] It trains normal patterns of voice production, rather than consciously correcting faulty vocal behaviour. In gradually more complex exercises, the patient copies the SLT's vocal model, thus developing kinaesthetic awareness of the desired control and coordination.[46] Emphasis in training is on producing easy voice with abdominal engagement in breath flow. Rhythmic consonant sound patterns called 'accents' are first used in slow, low-pitched exercises, then in faster, higher- and variably pitched tasks, and graduating in speech tasks. This method is shown to be effective with vocal fold lesions, vocal fold atrophy and muscle tension dysphonias.[47]

ESTILL VOICE TRAINING AND ALISON BAGNALL'S VOICECRAFT

Singer, voice researcher and teacher Jo Estill developed the Estill Voice Training (EVT) system, which enables individuals to gain isolated control over individual structures within the voice production system.[4] The structures include: head and neck, velum, lips, tongue, jaw, larynx, aryepiglottic sphincter, false vocal cords, true vocal cords, thyroid and cricoid cartilage, and torso. By controlling these structures in various combinations, different voice qualities are produced: for example, speech quality, twang and belting. SLTs guide the patient to develop kinaesthetic awareness of their vocal habits and of the muscular effort involved. By increasing this awareness and gaining specific motor control over relevant structures, the patient can identify and adopt more healthy and useful vocal behaviour. Singing teachers and voice coaches for professional voice users such as actors also use EVT to maximize voice control and function. Like EVT, Alison Bagnall's Voicecraft[1] focuses on teaching differential control of multiple parameters of the larynx and vocal tract.[48] Voicecraft is applied to and predominantly taught in the context of disordered voice. Clinical voice work of many SLTs in the UK is informed by Estill and Voicecraft training.[29, 30] There is a clear scientific basis and rationale for the work, as Jo Estill's extensive research data on aspects of EVT attests,[4] though there are as yet no published studies of systematic use of these interventions with a disordered voice population.

LARYNGEAL MANUAL THERAPY

SLTs use circumlaryngeal manual therapy, digital laryngeal manipulation, voice massage or laryngeal manual therapy (LMT) to manipulate the perilaryngeal area to redress muscle tension.[49–51] Methods of manual therapies vary but essentially focus on reducing excessive tension in the extrinsic laryngeal musculature. Initial palpation helps the SLT to note laryngeal posture (e.g. held high or forced lowered), muscle tone and pain or tenderness of muscle tissue. Areas the SLT may work on include sternocleidomastoid muscles, supra-laryngeal muscles, hyoid position and surrounding musculature, lateral laryngeal movement and rotation.[52] Evidence suggests manual therapies are an effective treatment for muscle tension dysphonia and can resolve even severe hyperfunctional dysphonia.[49–52]

LEE SILVERMAN VOICE THERAPY (LSVT®)

Lee Silverman Voice Therapy (LSVT®) has been developed to treat hypofunctional dysphonia associated with Parkinson's disease.[3] The aim is to alter phonatory effort and 'recalibrate' the patient's perception of effort and loudness levels in speech. SLTs encourage patients to 'think loud', and provide feedback with a decibel meter during repetitions of loud sustained vowels and other speech tasks. The programme is structured and intensive: patients attend individual sessions four times a week for a month, and practise at home in between sessions. LSVT is increasingly used with other hypofunctional dysphonias. It is contraindicated for use with patients with normal neurological function or hyperfunctional dysphonia and, if used inappropriately, may be harmful to both client and SLT.[38] The programme has been used with good results for Parkinson's patients with long-term effects, improving clarity of speech and overall speech intelligibility.[53]

LESSAC–MADSEN RESONANCE VOICE THERAPY (LMRVT)

Based on the work of Arthur Lessac and Mark Madsen, Katherine Verdolini-Abbott has developed a structured intervention programme to reduce aberrant vocal behaviour by establishing easy and clear or resonant voice.[39] SLTs encourage the patient to notice vibratory sensations towards the front of their face on certain voiced sounds (e.g. /m/). Patients practise forward placing of the voice in combination with a sense of ease of voice production in various speech tasks. Individual therapy sessions of 30–45 minutes take place once or twice a week over a 4–6 week period. Research suggests LMRVT is a useful approach in treating functional voice disorders and associated pathology such as nodules, and in improving vocal fold healing in acute inflammation.[54, 55]

SEMI-OCCLUDED VOCAL TRACT THERAPY (SOVT)

Flow phonation, 'lax vox' and SOVT are treatment approaches aiming to reduce muscle tension and hyperfunctional voice by altering air pressure levels in phonation.[56, 57] Exercises with straws, narrow tubes or lip-rounded vowels can improve vocal stability as phonation threshold pressures in the vocal tract are altered.[5] SOVT can train a patient with a hyperfunctional or 'pressed' voice to produce phonation with less effort and adopt more efficient and less effortful phonation. Principles of SOVT are present in other

voice interventions, such as the accent method, resonance therapy, and twang in Estill/Voicecraft.[56] These interventions are based on scientific and physiologic principles,[5, 56] and have long been present in voice therapy practice. The evidence base for lax vox and SOVT as intervention programmes with disordered voice populations is limited.

STEMPLE VOCAL FUNCTION EXERCISES (VFE)

Stemple vocal function exercises (VFEs) are based on a physiological approach[43] and centre on the principle of exercise to achieve optimal coordination of breath support, phonation and resonance, in combination with stamina and strength. SLTs encourage patients to produce 'quiet' (not projected) voice with a forward placement, sensed by the patient as a 'buzzing' of the lips. The programme is highly structured and requires patients to do specific exercises four times a day over 8–10 weeks.[2, 43] Exercises include a vocal warm-up, maximal pitch glides (low-to-high and high-to-low) and maximal vowel prolongations at different pitches. The standardized nature of the programme lends itself well to research, and the evidence base for this intervention is considerable.[43]

ECLECTIC VOICE THERAPY

In the UK, the Royal College of SLTs recommends that SLTs have an eclectic approach in voice therapy. Drawing on many of the above techniques and approaches, the skilled SLT targets the specific factors relevant to the individual with the voice problem, with an intervention approach that is uniquely suited to them. This approach is potentially the most holistic and client-centred. Unlike in a structured programme, in eclectic voice therapy no SLT would provide exactly the same intervention twice, even to an ostensibly 'identical' case of muscle tension dysphonia or vocal fold palsy. Eclectic voice therapy is based on sound clinical rationale and a thorough understanding of intervention strategies and underlying principles. Establishing an evidence base for eclectic voice therapy is methodologically challenging though not impossible, as shown by Mackenzie et al's randomized controlled trial in functional dysphonia.[32]

CONCLUSION

SLTs working with patients with voice disorders facilitate behavioural change in a principled way. Voice therapy encompasses a variety of patient-centred activities, resulting in demonstrable vocal improvement as shown by a range of outcome measures.

Review of the level of evidence in voice literature suggests there are small numbers of level 1 and 2 articles as compared with medical and otolaryngology literature.[58]

FUTURE RESEARCH

- The majority of voice research in the UK is produced by practising clinicians, resulting in clinically applied research.[17] The level of research in the field of voice is predominantly grade B, level 2 and 3, consisting mainly of effectiveness and some larger-scale efficacy studies. The evidence base for voice therapy continues to develop, with a need for future studies to be larger, methodologically sound, replicable and generalizable.[33, 40, 59]
- Suggested areas for future research include:
  - content of voice therapy in relation to pathologies
  - comparison studies of direct interventions with same and different pathologies.

KEY POINTS

- Voice therapy aims to:
  - restore voice
  - maximize vocal potential
  - assist in communication adjustments where voice improvement is likely to be limited by laryngeal structure.
- Voice therapy is based on:
  - systematic, multifactorial assessment of the voice
  - individualized goals for patients linked to assessment findings
  - joint planning with patient
  - a hierarchical treatment plan.
- Multifactorial assessment of current vocal behaviour includes:
  - phonatory physiology
  - perceptual voice rating (using GRBAS or CAPE-V rating scale)
  - patient-reported symptoms and their impact (questionnaires such as VHI, VoiSS and VPQ)
  - acoustic profile using instrumental measures of voice such as PRAAT and Laryngograph®.
- Intervention consists of a combination of direct and indirect treatment approaches.
- Types of direct voice therapy include:
  - accent method
  - Estill Voice Training and Voicecraft
  - laryngeal manual therapy
  - Lee Silverman Voice Therapy
  - resonance therapy
  - vocal function exercises.
- Voice therapy is often eclectic, where a skilled and experienced voice specialist may draw from a range of interventions based on sound clinical rationale to suit the individual's vocal needs.
- The evidence base for voice therapy is mainly at grade B with some level 1 evidence. Future studies need to be larger, methodologically sound, replicable and generalizable.

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CHAPTER 67

PHONOSURGERY

Abie Mendelsohn and Marc Remacle

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SEARCH STRATEGY

Data in this chapter may be updated by a Medline search using the keywords: voice, larynx, vocal fold and focusing on phonosurgery and results.

INTRODUCTION

Voice disorders are typically only appreciated by those afflicted with these conditions. While there have been great advances throughout the years within the diagnosis and treatment of voice disorders, we are still quite limited in the overall range of intervention available to the practitioners concentrating in this critical area. The last 50 years has seen an increased awareness and emphasis on vocal results and the expansion of phonosurgery, which is defined as 'any surgery designed primarily for the improvement or restoration of the voice'. Nowadays, 'surgery' refers to office-based procedures, interventions under light anaesthesia (conscious sedation), or surgery with general anaesthesia.

Prior to any surgical intervention, complete assessment of patients with a voice disorder should minimally include a complete history (typically as informative as the physical examination) and thorough physical examination. Critical aspects of the physical examination include lateral neck palpation, thyroid examination, observation of laryngeal elevation, tongue and palate mobility, respiratory status, and nasal examination. Once these areas are sufficiently evaluated, the larynx may then be imaged via office-based indirect laryngoscopy. Indirect laryngoscopes (either flexible or rigid) are preferably combined with video recording, which is of crucial importance for immediate review of physical findings as well as comparative evaluation following interventions. Stroboscopy has been a standard of vocal fold cover evaluation, though this technology is inherently weakened by its requirement of normal vibratory patterns, which is discussed in further depth in Chapter 61, Assessment and examination of the larynx and Chapter 62, Evaluation of the voice. High-speed videolaryngoscopy is a useful adjunct in the diagnosis of voice disorders. Additional examination modalities include laryngeal electromyography and voice measurements (both quantitative and qualitative). The formation of multidisciplinary voice clinics allows an academic and scientific approach to voice disorders and greater emphasis on an evidence-based approach to laryngology.

Like any surgical intervention, phonosurgery should be considered the very last treatment option once all conservative measures have either failed to improve the voice or they are deemed inadequate based on our understanding of certain pathologic conditions. Too quickly taken to the operating theatre, patients may end up in worse situations both vocally and medically following unnecessary surgical interventions. A helpful philosophy is to approach potential patients as if attempting to convince those patients away from surgery; and in this manner only the most necessary pathologies will be exposed to the risks of surgery.

As glottic cancer is discussed in Chapter 14, Tumours of the larynx, our discussion of phonosurgery will be limited to benign disease. The topics that will be discussed include microlaryngeal surgery, injection laryngoplasty and laryngeal framework surgery (including nerve grafting).

MICROLARYNGOSCOPY

History

Claudius Galen is credited with recognizing the larynx as the organ responsible for voice production in the second century of the common era. Avicenna (Abu Ali al-Husain ibn Abdullah ibn Sina), recognized as one of the fathers of modern medicine, in the 10th century described in detail the muscular control of the laryngeal cartilages, including an in-depth discussion regarding the role of the corniculate and cuneiform cartilages. In the 1700s the science was advanced with Giovanni Morgagni's connection between vocal fold pathology and dysphonia. Although Manuel Garcia[1] is often credited with the first description of mirror indirect laryngoscopy, Bozzini[2] was actually the first to report on mirror visualization of the larynx and indeed described the first indirect laryngoscope for surgery on the vocal folds. Indirect laryngoscopic surgery was the norm at the beginning of the 19th century and may have played a role in the well-documented tale of Morell McKenzie and the transoral management of laryngeal cancer in Crown Prince Frederick. At that time, there was fear that transoral laryngeal biopsies could induce cancer of the larynx and as a result laryngeal diseases, such as tuberculosis and syphilis, were often treated by an open procedure with or without a tracheostomy. These were associated with a high morbidity and even mortality and there is postulation that Virchov purposely misdiagnosed Prince Frederick's carcinoma because he was aware of Van Bergman's (the prince's surgeon) abysmal survival statistics following total laryngectomy.[3] Horace Green described the first direct laryngeal surgical case, which was the removal of a laryngeal polyp in an 11-year-old girl.[4] Due to the fact that in a child the larynx is in a high position, Green was able to use a bent tongue spatula and sunlight to obtain direct vision and remove the polyp. Oskar Kleinsasser described the adaptation of the microscope to direct laryngoscopy allowing for fine manipulation of the vocal folds. Since then, numerous developments and modifications have taken place but all demonstrate the fundamental phonosurgical principles as detailed in this chapter.

Anatomy

A knowledge of the anatomy of the larynx, specifically the microarchitecture of the vocal folds is essential (**Figure 67.1**). The layered structure of the vocal fold and the different mechanical and physical properties of each layer allow for the unique capacity for continuous vibration (or entrained oscillations). While the true mechanics of vocal fold vibration is still beyond our full understanding and requires active investigation, it is critical that this unique microarchitecture is preserved as its loss (i.e. vocal fold scar) results in the dramatic loss of voice quality. Vocal fold epithelium is the first identified layer of the vocal fold. The mucosa is comprised of stratified squamous epithelium, which transitions to pseudocolumnar cells superiorly into the laryngeal ventricle and inferiorly when the glottis transitions to the subglottis and trachea. The epithelium thickness is approximately 50 microns. The limited depth of the epithelium prevents physical manipulation of this layer alone. Surgical interventions designed to excise, or lift, the epithelium therefore requires some level of manipulation of the lamina propria. The specific layering of the human lamina propria is unique amongst mammalian species. The lamina propria is divided into

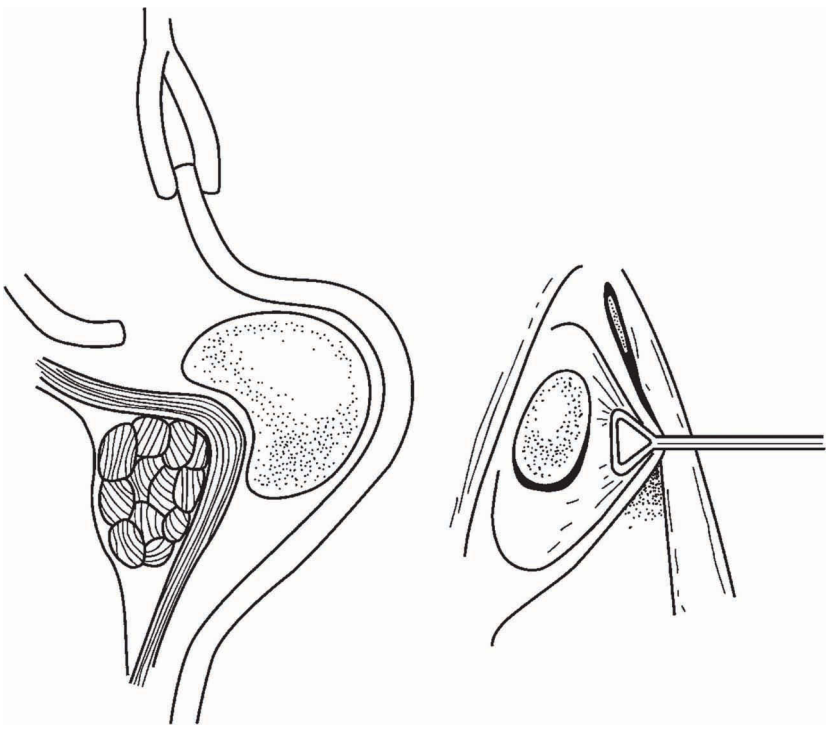

Figure 67.1 Intracordal cyst approached via cordotomy and mucosal flap.

three components: superficial, intermediate and deep. The main component of the lamina propria is collagen fibres. The composition of collagen fibre type and the fibre density distinguishes the three layers of the human vocal fold, which transitions from less-to-more dense structure extending from the superficial to deep. Depth of the superficial lamina is 0.14 mm in women and 0.30 mm in men. The vocal ligament is typically defined as the combined structure of the intermediate and deep layers of the lamina propria, which is readily identified histologically as well as microsurgically.

Exposure

A flexed cervical-thoracic junction and extended atlanto-occipital joint, described by Chevalier Jackson, is now returning as the accepted position for microlaryngoscopic surgical access (**Figure 67.2**). Individual anatomic variations may require departure from this recommended patient position, including flexion at both cervical points, which can be easily modified prior to commencing vocal fold manipulation. Anatomic variations are also optimally managed through the use of different sized (length and diameter) and style (e.g. anterior lip, distending) rigid laryngoscopes. It is critical for the laryngologic surgeon to have several laryngoscopes available for each surgery. Difficult cases can be improved through external laryngeal counter pressure, which can be done either with an assistant's fingers or gauze padding and elastic tape.

Instrumentation

Proper instrumentation, in addition to the laryngoscopes discussed, is required. Microlaryngeal instruments need to be fine, sharp and well maintained to allow precise manipulation of the vocal fold to limit scarring risk. The authors utilize atraumatic soft tissue microlaryngeal forceps (i.e. Bouchayer forceps) in a vast majority of surgeries. Manipulation and trauma to areas beyond what is absolutely necessary will undoubtedly increase scarring and thereby negatively impact post-treatment voice quality. Limiting the area of surgery not only applies along the periphery, or along the surface, but the deep extent of surgery should also be limited to what is absolutely necessary.

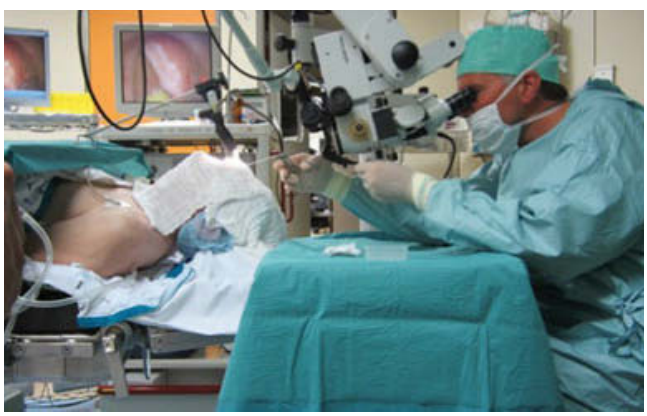

Figure 67.2 Microlaryngoscopy set-up. The patient is positioned with the recommended cervical flexion and extension. Laryngoscope is suspended by fulcrum suspension bar.

Benign disease is usually located in the mucosal layer or in the superficial part of the lamina propria. Surgery should, therefore, be superficial, staying out of the vocal ligament, with limited mucosal excision only. There is no role for stripping of the mucosa of the vocal fold for benign disease, and vocal fold preservation should be the paramount concern of phonosurgery for benign disease.

Lasers and technologic instrumentation

The laser is not merely a precise surgical knife and the surgeon must have an understanding of the effects of wavelength spot size, wattage and mode (pulsed or continuous), their soft tissue interaction and the important hazards linked to their use. Currently, the three most widely utilized laser types include CO_2, potassium titanyl phosphate (KTP) and diode. The specifics of each laser type can be found in Chapter 50, Laser principles in otolaryngology, head and neck surgery, but it is critical that the laryngologic surgeon understands all aspects of the wavelength, spot size and power settings of the utilized laser before attempting even the smallest of procedures. Benninger[5] described a prospective study on patients using the CO_2 laser and microsurgery and came to the conclusion that in a trained laryngologist's hands, both are excellent tools in the management of phonosurgical disorders. In many ways, laser and cold instruments should be considered as synergistic tools rather than in direct opposition. It is, therefore, a personal choice but the authors prefer to limit laser to vascular lesions or those that bleed on removal, such as papillomatosis or granulomas, or to the removal of cartilage and when excising large areas of tissue. Although the laser plume in the management of papillomas has been considered a potential risk of infection, this risk is only theoretical and no case report for this type of infection exists.

Some surgeons now advocate the use of power instrumentation, such as the laryngeal microdebrider. The microdebrider has been used for various laryngeal lesions including papillomas and there is an early report using subjective methods that patients have less post-operative pain and a quicker return to a usable speaking voice.[6] Others have used the debrider for polyps and Reinke's oedema, and also for removing tumours at both glottic and subglottic levels. Once again, one must be aware of the microanatomy of the vocal folds and the principles of phonosurgery and whether accurate depth of resection can be made with this tool. A suction collection pot must also be used to confirm histological diagnosis but margins and orientation of the specimen are lost with this technique.

Anaesthesia

General anaesthesia is the norm for microlaryngeal surgery although there have been some articles describing indirect phonosurgery under a local anaesthetic with stroboscopic control[7] or direct laryngoscopy with nerve blocks and topical anaesthesia. These techniques have

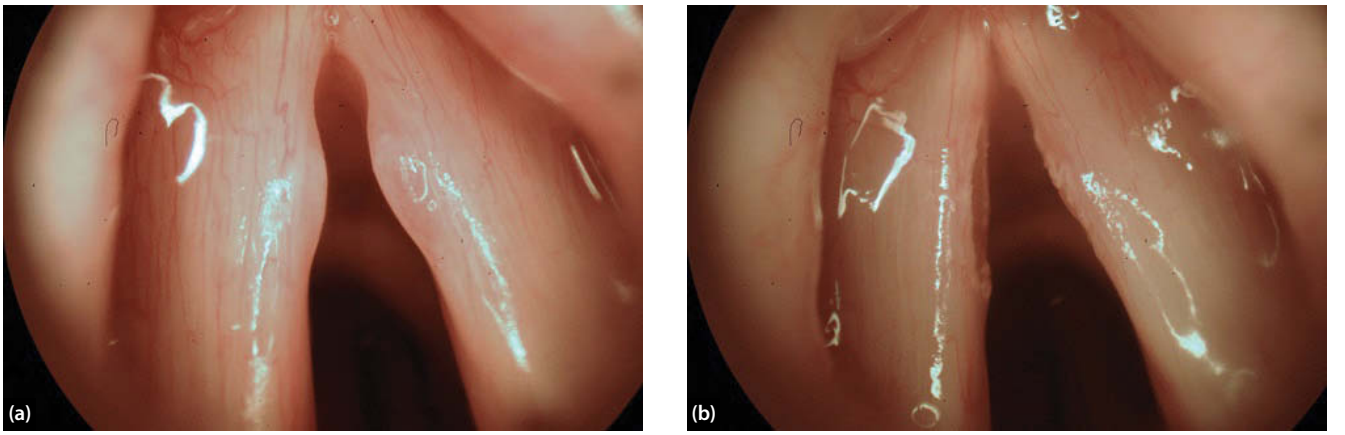

Figure 67.3 Vocal fold nodules. The patient demonstrates bilateral and symmetric phonatory lesions along the anterior one-third of the membranous vocal volds **(a)**. After voice therapy, the nodules persisted and the lesions were resected with CO_2 laser phonosurgery **(b)**.

not been widely accepted. General anaesthesia may be induced and maintained through three main techniques: intubation, apnoea or jet ventilation. Standard oral-tracheal intubation is to be performed only by the most experienced anaesthesiologists as unwanted vocal fold manipulation may impart more phono-damage than then planned phonosurgical procedure. General anaesthesia is typically recommended so muscular relaxants (paralytic agents) can be administered to maintain motionless vocal folds during surgery. Endotracheal tube choice should be made in consultation with the treating anaesthetist, though the endotracheal tube with the smallest outer diameter that can offer safe respirations should be utilized. The authors rarely utilize endotracheal tubes larger than size 5.0 during phonosurgery. Additionally, when available, micro-laryngoscopy tubes (MLT) should be requested to improve the overall length of the tube with smaller diameters. If laser is used during surgery, a laser-safe endotracheal tube should be placed, again with the smallest possible outer diameter, and the tracheal balloons filled with normal saline. Apneic technique calls for intermittent ventilation either by mask ventilation or intermittent endotracheal intubation to oxygenate and ventilate the patient, and the patient is left without active respiration during the phonosurgery. This technique is useful when the lesion is in the posterior glottis, where endotracheal tube would otherwise be visually obstructing and jet ventilation is otherwise not indicated or not available. Jet ventilation offers the best exposure of the larynx and can be performed for prolonged periods. Jet ventilation should *not* be used in cases where bleeding is expected as there is no barrier for aspiration of the blood.

Post-operative voice rest

Although there are no control studies looking at the role of voice rest in recurrence and healing, it is now a generally accepted rule that 48 hours of absolute voice rest following a phonosurgical procedure is essential. The authors recommend a minimum of 7–10 days of strict vocal rest followed by resumption of voicing under the guidance of voice pathologists.

Pathology

NODULES

These are bilateral lesions of functional aetiology and the vast majority resolve completely following compliant voice therapy. They are found at the midpoint of the vocal folds (membranous vocal cord) and are confined to the superficial squamous epithelium. Histopathological studies show thickening of the basement membrane together with areas of haemorrhage, fibrin deposits and hyalinization. Their aetiology is associated with phonatory strain and a stroboscope can be useful in distinguishing this pathologic entity from others that are more readily treated with phonosurgery. In the very rare situation where true vocal fold nodules do not respond with compliant treatment, surgery may be offered to remove these lesions. It must be restated that patients who are non-compliant with their voice therapy should not have surgery offered as their poor vocal behaviours will undoubtedly cause poor healing and scarring, which is a situation more challenging to treat than nodules. During surgery, the centre of the nodule is held with atraumatic forceps and pulled medially towards the opposite cord. The mucosa is cut at its base, by cold instruments or laser, producing a straight vibratory edge and preventing secondary notching. The opposite nodule can then be removed in a similar fashion, taking care not to damage the mucosa of the anterior commissure. There is no contraindication to removing both nodules at the same time using this precision technique.

POLYPS

These are usually unilateral, localized areas of oedematous tissue although some may be angiomatous and may also contain areas of haemorrhage. Though a trial of voice therapy is indicated, these lesions are more likely to require phonosurgery than nodules. The site of the lesion is again superficial to the vocal ligament and careful examination may show a contact response on the contralateral vocal fold, which should rarely be addressed. Gentle, steady traction is applied by grasping forceps towards the opposite cord and the base of the polyp is sectioned.

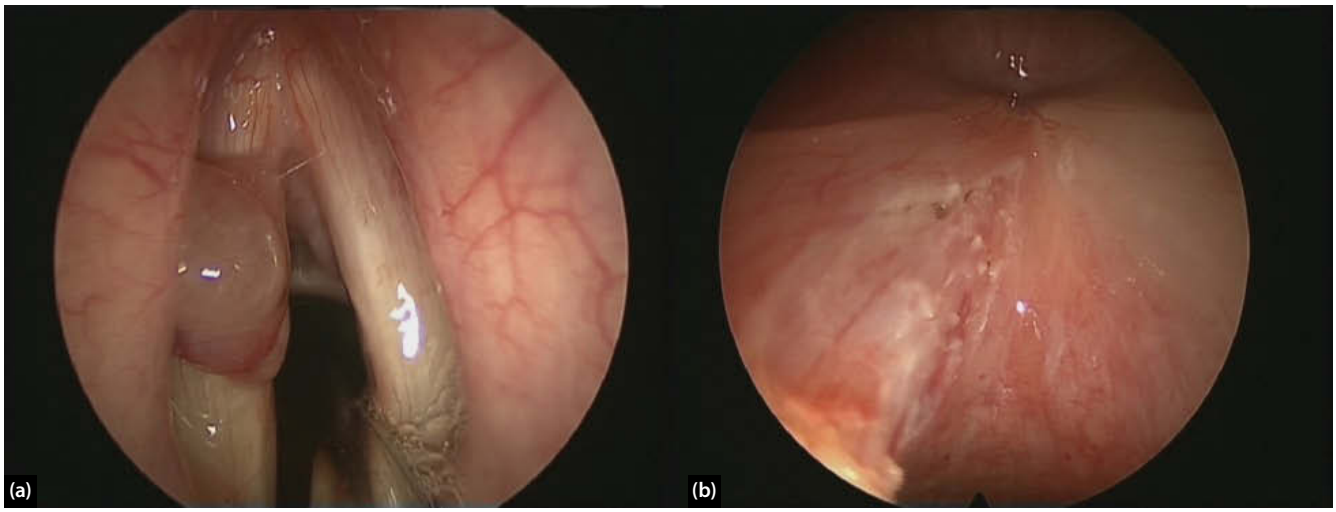

Figure 67.4 Vocal fold polyp. The patient demonstrated left vocal fold polyp at the mid-membranous portion of the vocal fold. CO_2 laser excision preserving the cover layer will allow for excellent healing. (70° endoscopic view.)

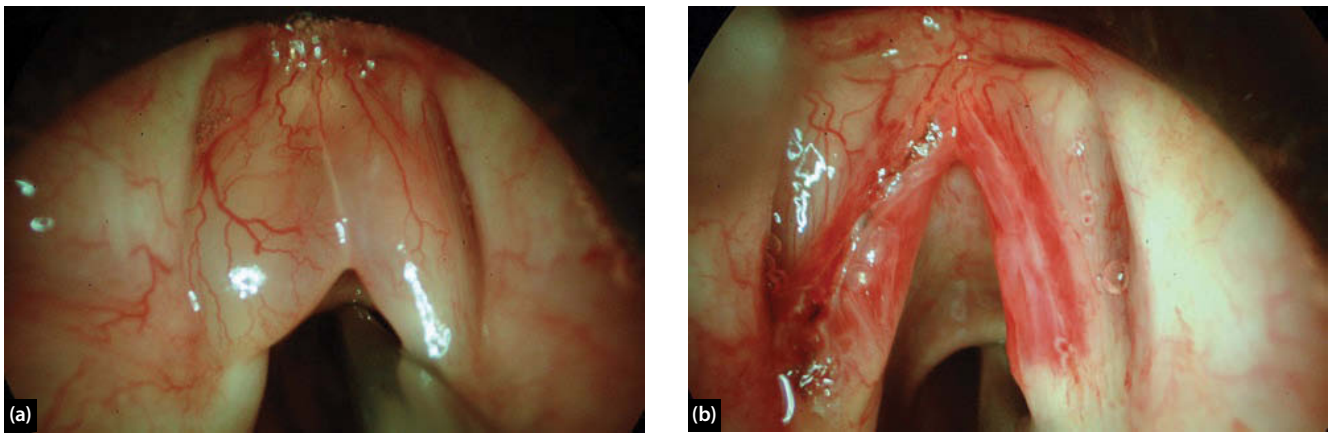

Figure 67.5 Reinke's oedema. The patient demonstrates severe oedema of the vocal fold cover along the anterior-posterior length of the membranous portion of the vocal folds **(a)**. Phonosurgery utilizing CO_2 laser excision of the oedematous tissue preserving the cover layer will allow for excellent healing **(b)**.

Preservation of mucosa is essential, too little resulting in reformation of the polyp, too much resection giving a notched, scarred cord with tethering of the layers of the vocal fold, as seen in **Figure 67.4**.

REINKE'S OEDEMA

This is a bilateral diffuse condition where there is a collection of polypoidal tissue in the superficial layer of the lamina propria, as seen in **Figure 67.5a**. This condition is almost universally associated with cigarette smoking. Patients who continue to smoke should be considered poor surgical candidates as this condition has a high likelihood of recurrence with continued smoke irritation. The pathophysiology is suggested to stem from the poor lymphatic drainage of the vocal folds resulting from the unique embryological origins of the supra and subglottic areas. This poor lymphatic drainage, however, is also advantageous by giving a good prognosis for small glottic tumours. Incision is made on the lateral aspect of the superior surface of the vocal fold with micro-scalpel or laser. The median vibrating edge of the vocal fold is, therefore, preserved. Mucosa is then elevated with a blunt dissector and myxomatous contents either aspirated (suctioned) or removed with cupped forceps. Care must be taken to avoid damaging the vocal ligament or traumatizing the overlying mucosa with excessive suction. Following removal of the contents, the mucosal flap is replaced and any excess epithelium trimmed with microscissors, as seen in **Figure 67.5b**. The mucosal flap can be laid on the surface and left to heal by surface tension, suturing or tissue glue (autologous or commercial) used to hold this in place. Providing care is taken in the region of the anterior commissure, there is no contraindication to operating on both folds at the same time.

INTRACORDAL CYSTS

These primarily surgical lesions may be either secondary to mucosal retention or epidermoid cysts, and stroboscopy has greatly increased the ease of diagnosis, though it remains an ultimately a very challenging diagnosis at times.

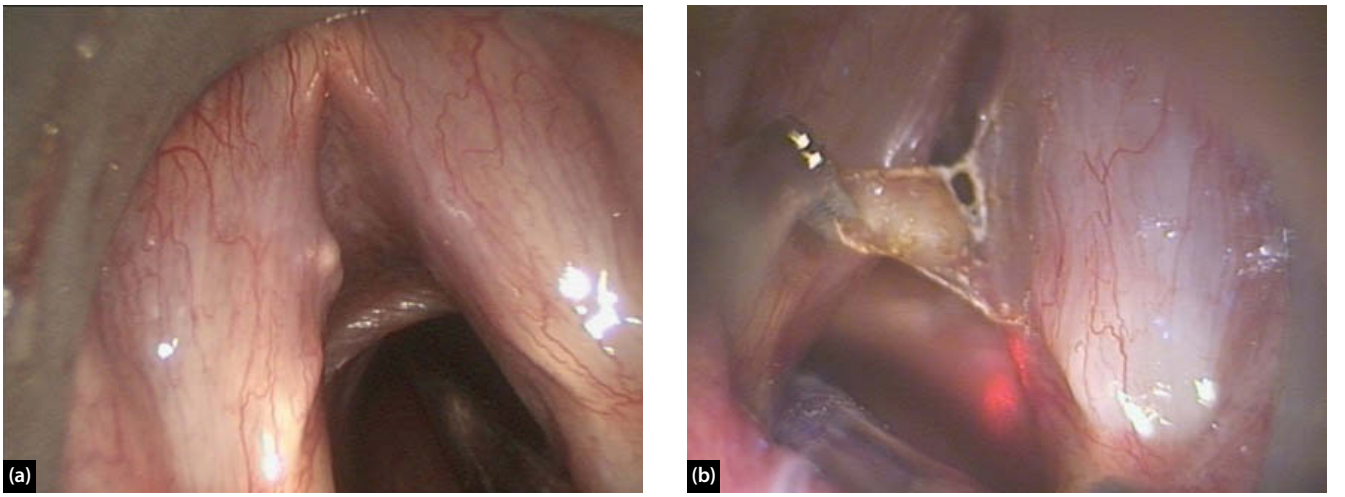

Figure 67.6 Intracordal cyst. The patient demonstrates a right mucous retention cyst at the mid-membranous point of the vocal fold **(a)**. Also seen is intra-operative view of a cyst being dissected from the vocal fold cover by CO_2 laser **(b)**.

The mucous retention cyst is found in the cover of the vocal fold and can be removed either with cold instruments or with the laser, but again remaining superficial to the ligament. An epidermoid submucosal cyst can be approached via a lateral microflap where an incision is made on the superior surface of the vocal fold away from its medial edge. The flap is then elevated from lateral to medial, the lesion excised and the flap replaced. There are good quantitative results in phonosurgery following this approach although some debate exists as to whether there is damage to the basement membrane when elevating the flap. Blood vessels have been identified in the flap and would suggest that the plane of dissection should be deep to the basement membrane, therefore objections of greater damage to the basement membrane may not be founded. As a result of this work, however, Sataloff et al.[8] devised a mini microflap, which involves elevating a small section of epithelium directly over the lesion via a medially based incision as seen in **Figure 67.6**. They also report good results both subjectively and quantitatively using this method.

VOCAL FOLD VARICES

These are often considered a potential source of haemorrhage but in most cases, if lying in a longitudinal orientation, they can be left and treated conservatively unless recurrent haemorrhage occurs. The presence of vessels lying at 90 degrees or at a different orientation may indicate underlying disease, possibly neoplastic, and require further investigation. Recurrent haemorrhage from these vessels can be dealt with either by lasering the blood vessel or needle cautery to ablate the vessels. Angiolytic lasers such as KTP or pulse-dye lasers can be of particular utility with these lesions.

ANTERIOR WEBS

If these are small and thin, they can be divided either with a laser or with cold steel. A microweb is frequently associated with vocal cord nodules[9] and can be removed at the same time. Thick webs have a 50% chance of recurring following laser excision and may require insertion of a keel, either endoscopically or via an open procedure, to prevent recurrence. A local mucosal flap covering the exposed tissue on one side has also been reported.[10]

GRANULOMAS

These are located on the vocal process of the arytenoid cartilage and are usually unilateral, sessile, bilobed lesions. Aetiologic factors include endotracheal intubation, trauma, pharyngolaryngeal reflux, hyperfunctional voice disorders and combinations of these factors. The characteristic posterior position in the glottis is diagnostic and tissue diagnosis is rarely indicated. Granulomas frequently recur following surgery alone. The primary treatment for unilateral granuloma is therefore bilateral vocal fold injection of botulinum toxin (Botox) to the adductor muscle groups, similar to the treatment of adductor spasmodic dysphonia. However, the dose is about 10-fold higher when treating granulomas. Patients must be counselled regarding the 3-month period of decreased vocal loudness, though this pharmacologic-induced voice rest is critical for complete resolution of even moderate to severely hypertrophic granulomas. Botox injections must be coupled with conservative measures including aggressive laryngopharyngeal reflux treatment and voice therapy. Some granulomas present at such an advanced stage, where airway obstruction is a concern. Such lesions can be excised through phonosurgery, though the vascularity of these lesions typically requires the use of laser energy instead of cold instruments. However, Botox injections should still be administered at the time of resection to reduce the risk of recurrence.

PAPILLOMA

These neoplastic lesions are due to the human papilloma virus (subtypes 6 and 11) and frequently recur. They are

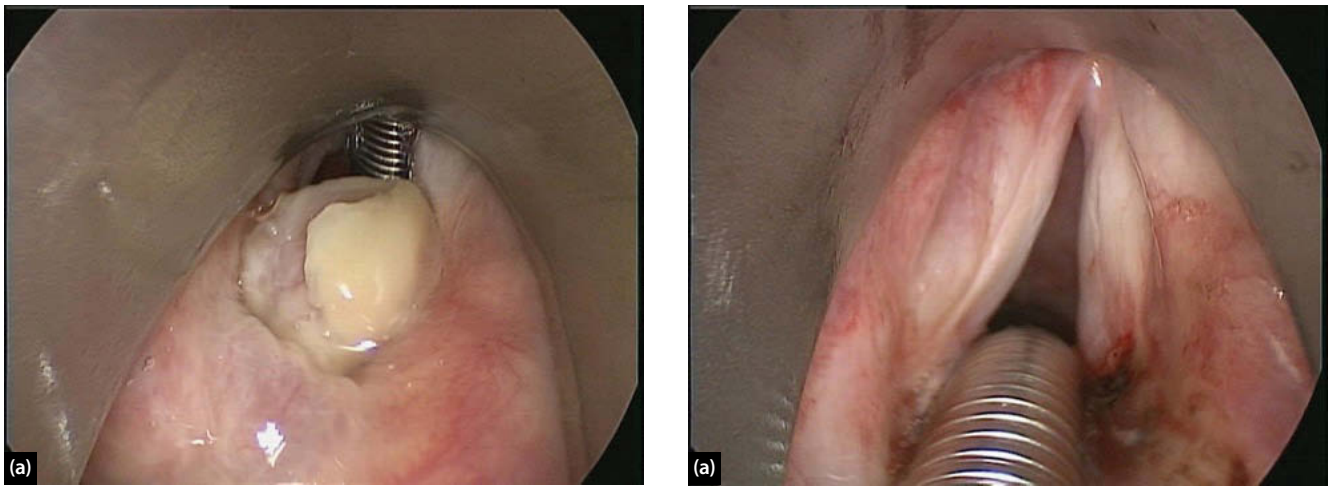

Figure 67.7 Granuloma. The patient demonstrates a large right vocal fold granuloma arising from the posterior glottis and obstructing the glottal space **(a)**. Following excision by CO_2 laser, the glottis is then clear of obstruction **(b)**. Importantly, the adductor muscle groups were treated with Botox injections bilaterally.

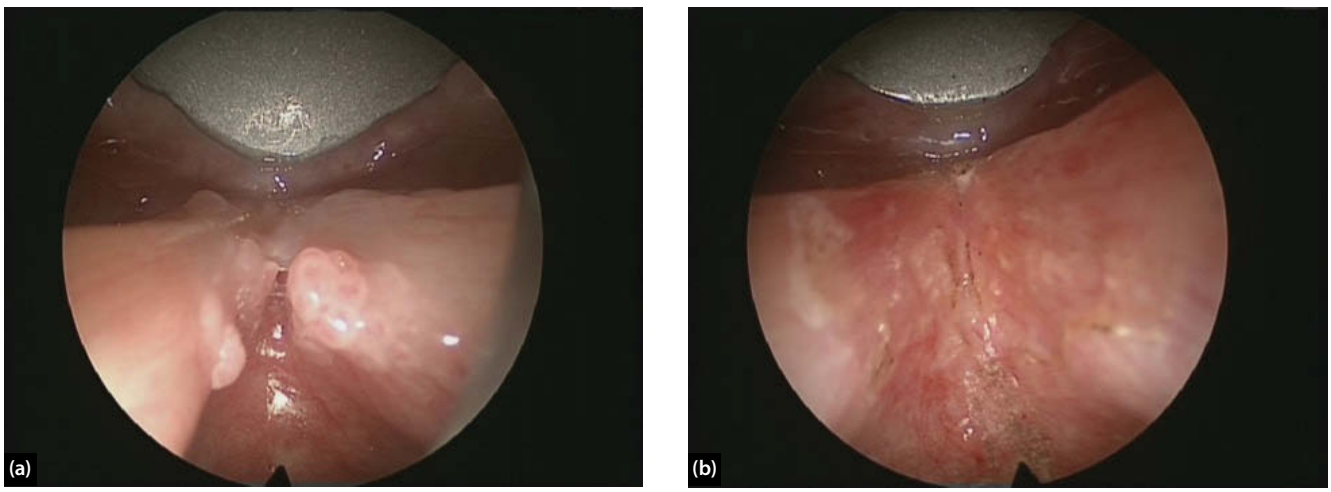

Figure 67.8 Papilloma. The patient demonstrates sessile papillomatosis of the membranous vocal folds bilaterally involving the anterior commissure **(a)**. Following ablation by CO_2 laser, vocal fold cover is preserved **(b)** (70° endoscopy).

often found at areas of transition in the upper aerodigestive tract where there is increased air turbulence, drying and cooling of mucosa, and at the change of ciliary to squamous epithelium.[11] CO_2 laser excision is the treatment of choice in the authors' hands, with minimal trauma to surrounding tissue (that may contain dormant virus). An endoscope with a smoke evacuation channel is useful. Single papillomas are grasped gently as they may be friable and the laser is used to excise the base. Surgical techniques for multiple papilloma include using injection of saline (+/– epinephrine) submucosally (hydrodissection) and excising the mucosa *en bloc*. This gives a lower recurrence rate than surface ablation. It is also (by addressing the principles of phonosurgery and remaining superficial to the ligament) less likely to give scarring by better definition of tissue planes, as seen in **Figure 67.8**. Many case reports in the past have reported success of different treatments by the frequency of repeated lasering but there are now many established scoring systems taking into account the distribution and appearance of papillomas in recognized areas of the larynx. This allows a more scientific and quantitative approach to future treatments. There is encouraging work looking at an immunodeficiency of T-cell lymphocytes in patients with papillomas and the use of adjuvant treatments, such as retinoids, alpha interferon, ribavirin, cyclooxygenase 2 inhibitors, and cidofovir. Photodynamic therapy is also in its experimental stage.[12]

VOCAL SULCUS

This is a groove along the mucosa and can be classified into three types: the first is a physiological or pseudosulcus often associated with reflux; the second is a sulcus vergeture, which goes down to the superficial layer of the lamina propria; and the third is a sulcus vocalis going down to the deeper layers of the ligament. There is a theory that a sulcus is related to ruptured congenital cysts and may well be more common in the Indian subcontinent. They frequently present with persistent dysphonia following puberty. Numerous phonosurgical approaches

have been suggested from excising the sulcus to injecting collagen or fat to boost the underlying layers. Pontes[13] advocates a technique involving parallel mucosal incisions of varying lengths running in a cephalad to cordal direction to break up the linear scar of the vocal fold. A lengthy post-operative recovery time may be required, sometimes up to a year. Despite the above, no treatment has been demonstrated to be reliably effective for this frustrating cause of dysphonia.

BEST CLINICAL PRACTICE

- ✓ Nodules:
  - ✓ Nodules are managed by speech and language therapy with compliant voice therapy and laryngopharyngeal reflux therapy.
  - ✓ Rarely, surgical removal is indicated and involves grasping the centre of a nodule, pulling it medially and then using microscissors to cut mucosa close to the base, thus preserving normal mucosa and keeping a straight vibratory edge.
- ✓ Polyps:
  - ✓ During phonosurgery, excess mucosa is resected by laser or cold instruments resulting in smooth medial surface.
- ✓ Reinke's oedema:
  - ✓ Only following smoking cessation may surgery be offered.
  - ✓ Surgical intervention involves:
    - making a cordotomy incision on the superior aspect of the vocal fold (preserving the median vibrating edge)
    - elevation of the mucosa and aspiration or removal of the myxoedematous contents
    - replacing the mucosal flaps and trimming excess epithelium
    - laying flap onto surface and leaving it to heal by surface tension.
  - ✓ There is no contraindication to operating on the contralateral fold at the same operative setting.
- ✓ Papillomatosis:
  - ✓ Papillomas are recurrent and excised as needed.
  - ✓ Options for excision include CO_2 laser, angiolytic laser, or a microdebrider.
  - ✓ Further studies are required to address best frequency of treatment.
  - ✓ Adjuvant treatments include retinoids, alpha interferon, ribavarin, cyclooxygenase 2 inhibitors and cidovir, but additional trials are required to establish these treatments as standard of care.

KEY POINTS

- Use of surgical lasers requires understanding of the effect of spot size, wattage, mode, soft tissue interactions and hazards.
- Choosing CO_2 laser or cold dissection are a matter of clinical need and experience.
- Powered instruments, such as the microdebrider, can eliminate the risk of laser plume in infected cases, for example, when dealing with papillomatosis.

VOCAL FOLD INJECTION

Brunings[14] was the first to describe injection of the vocal folds in 1911 when he injected paraffin via a direct laryngoscopic approach under local anaesthesia. It is Arnold[15] in 1962, however, who popularized this technique and the introduction of Teflon. Since then, numerous materials have been introduced and some of these are listed in this section.

Materials

TEFLON

Teflon is discussed here for its historical importance only. There is no clinical indication in which its use justifies the risk of soft tissue reaction.

Teflon is a polymer of tetrafluoroethylene and is sold as a paste consisting of 50% glycerine. The glycerine component is absorbed in the first few weeks and its volume is partially replaced initially by an acute inflammatory reaction and later by a localized chronic inflammatory response, which encapsulates the remaining Teflon. This is, in effect, a localized granuloma but the difference in the initial volume injected and the final space-occupying lesion is unpredictable, which may cause a good immediate result to deteriorate with time. If Teflon is incorrectly placed superficially and erosion of the overlying mucosa occurs, this can lead to a granuloma on the surface of the vocal fold, and a 36% incidence of granuloma production has been reported. Teflon particle sizes in the paste are sold as 50–100 microns, too large for immediate lymphatic spread since macrophage lymphatic cut-off is 40 microns. Studies on a commercial preparation of Teflon, however, have found particles of 4–40 microns, which must lead to the question of distal spread. A study on Teflon injection into the peri-urethral areas has shown spread to both regional and distal organs via venous channels, but although local spread to lymph nodes and the thyroid gland has been demonstrated with laryngeal injection, no distal spread has yet been documented.

Removal of Teflon granulomas with a CO_2 laser gives high thermal damage and the vocal fold is scarred to such an extent that poor voice is almost guaranteed. As a result, excising the Teflon via an external approach and using a local muscle flap has been described with good results.[16]

FAT

This autogenous material has numerous advantages: it is easily harvested, readily available and does not give a foreign body reaction. There is no unified technique for its harvesting, with some authors recommending liposuction (which can lead to up to 30% cell destruction and an increased hypersensitivity reaction) whilst others harvest through a larger incision followed by irrigation with saline and soaking in insulin. However, universally, fat injection requires the morbidity of the harvesting site. It is reported that 30–50% of this fat will be absorbed within the first month and long-term studies also suggest a decrease in

volume with time.[17] As a result of its absorption, many suggest overcorrection at the time of injection. The material is of high density and requires insertion deep into the vocal fold. Encouraging quantitative voice results have been reported post-injection.

GLYCERINE

This can be used as a temporary material as it is absorbed within the first 2–6 weeks. It is completely reversible and frequently combined with laryngeal electromyography (EMG) in cases of a temporary paralysis. The EMG can be used prognostically to look at reinnervation of the vocal fold and the glycerine, by augmenting the paralyzed fold, allows glottic closure. Once again, its site should be deep within the muscle of the vocal fold.

COLLAGEN

This protein is a natural constituent of the lamina propria of the vocal fold. Widely used in dermal augmentation, it has been popularized by Ford et al. for use in the larynx where it becomes incorporated and even assimilated by new host tissue.[18] A cross-linkage ensures better stability and reduces the rate of hypersensitivity, which is <1%. Skin testing pre-operatively is recommended before the collagen is injected superficially into the vocal ligament. It is a challenging procedure with blanching of the vocal fold mucosa if too superficial. Although excellent results are reported by Ford, others have found this technique difficult and noted irregularity in its mode of absorption and replacement.

SILICONE

Bioplastique is a silicone gel consisting of vulcanized polydimethylsialoxane particles ranging from 150 to 600 microns suspended in hydrogel. After an initial acute inflammatory reaction, the material develops a fibrous capsule[19] and, although not used in the United States, it has been used sparingly in Europe. Location of the material should be deep within the body of the vocal fold but so far there are few long-term results on the quality of voice or any complications with migration.

CALCIUM HYDROXYAPATITE

Radiesse voice implant is a solution of calcium hydroxyapatite carried in an aqueous gel allowing for injection through small gauge needles (25G or 27G). It has found widespread usage since the commercial supply of bovine collagen has been limited. The most critical aspect of this material is a deep injection as superficial implantation will lead to long-term hoarseness.

Selection of operative methods

These may be subdivided as follows:

- general anaesthesia: (direct laryngoscopy)
- local anaesthesia: (indirect laryngoscopy):
  - transcutaneous route through the cricothyroid membranes
  - transcutaneous route through the thyroid cartilage
  - transcutaneous route through the thyrohyoid membrane
  - transoral route.

GENERAL ANAESTHESIA

Drawbacks include visualization problems due to the anaesthetic tube or some other means of ventilation, the abnormal anatomical position of the neck, difficulty in gaining access to the larynx in patients with cervical spine problems or other anatomical factors preventing direct laryngoscopy and, most significantly, lack of patient feedback via phonation during injection. This last factor plays an essential role in deciding the amount of material to inject at the time of surgery in patients undergoing procedures under local anaesthesia. Advocates of injections under general anaesthesia argue that physical manipulation of the injection material following injection can lead to a more uniform and wider area of medialization.

LOCAL ANAESTHESIA

Injection laryngoplasty is also routinely performed under local anaesthesia with the guidance of real-time visualization, typically through nasolaryngeal flexible laryngoscopy. The laryngologist typically practices a single injection site most frequently, but should be comfortable utilizing any of the described techniques as variation in patient comfort and anatomic composition will require alterations of the method. Transcutaneous techniques maintain the benefit of being procedures that can be carried out in the office with minimal time commitment for both the provider and patients.

There are three well-described transcutaneous methods. First, a transcutaneous piercing of the thyroid cartilage is typically the most straightforward approach to injection laryngoplasty. Penetration should be through the inferior half of the thyroid cartilage but difficulty can occur when the cartilage is ossified or the needle bore is blocked with cartilage. Penetrating the cricothyroid membrane is becoming a more familiar technique now that botulinum toxin injections into the thyroarytenoid muscle for adductor spasmodic dysphonia are increasing. The injection needle can either pass directly into the cord without entering the laryngeal lumen or pass initially into the lumen and then penetrate the fold whilst being visualized via a nasendoscope (**Figure 67.9**).[20] The transcricothyroid membrane approach is similar in its approach and if ossified thyroid cartilage ala is identified then the needle point is angled inferiorly to tuck under the inferior edge of the thyroid cartilage and an audible click is usually heard once the membrane is penetrated. The needle should then immediately be angled superior-laterally to find a position deep within the adductor muscle group. The transthyrohyoid method requires topical anaesthesia of the glottis (typically topical 4% lidocaine) before injection. Following adequate anaesthesia the needle is placed at the thyroid notch and

angled immediately inferiorly. Under direct visualization, the needle tip is seen exiting the petiole mucosa at midline to enter the supraglottic lumen. Following this, the needle tip can be guided under visualization laterally into the deep adductor muscle group where laryngoplasty can be performed. Finally, with the use of a rigid curved cannula (Abraham cannula), a needle may be guided transorally following adequate mucosa topical anaesthesia to achieve direct injection into the superior surface of the lateral vocal fold.

KEY POINTS

- Injectible materials include autologous fat, glycerine, collagen, silicon, and calcium hydroxyappatite.
- All provide immediate results, though optimal voicing may take 3 days for the injectate to even out.
- The provider must have comfort with multiple injection methods as individual patient needs and anatomy will require variability in planned approaches.

LARYNGEAL FRAMEWORK SURGERY

Payr,[21] in 1915, is credited with the first description of laryngeal framework surgery. This has been refined over many years by other surgeons but Isshiki[22] was the first to describe using an alloplastic material (Silastic) and also to stress the benefits of carrying out the procedure under a local anaesthetic using the patient's voice for feedback. His name, and the classification of laryngeal framework surgery into four types of thyroplasty, remain as shown in **Figure 67.10**.[22]

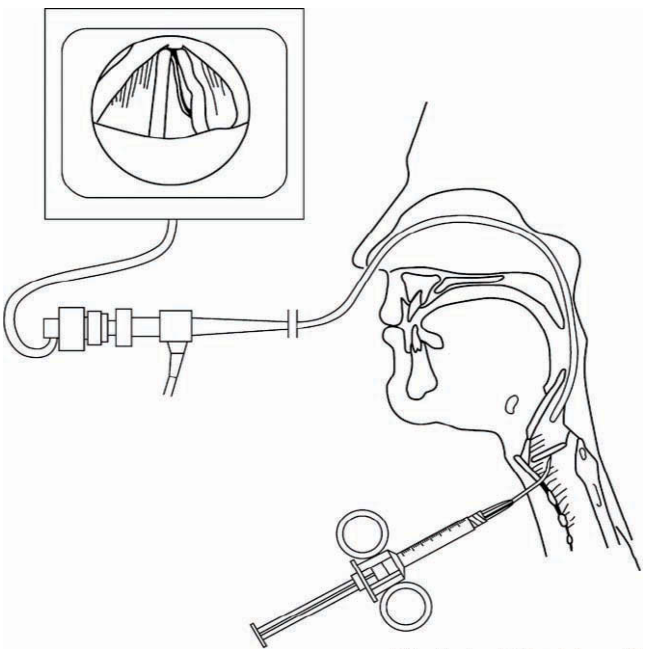

Figure 67.9 Transcutaneous technique with nasolaryngeal flexible laryngoscopy.

Laryngeal framework surgery allows the size of the glottic aperture, plane of closure of the vocal folds and vocal fold length to be modified. Laryngeal framework surgery also maintains the laryngeal dynamics without invasion of the vocal folds and alteration of their mass or stiffness.

Selection of patients

Type I, or medialization thyroplasty, can be performed for patients with a unilateral vocal cord paralysis. Waiting 12 months in idiopathic cases is recommended for possible spontaneous recovery of vocal fold motion. Injection laryngoplasty should be provided within this initial time period to allow for adequate voicing and cough. Medialization thyroplasty can also performed bilaterally in cases of bilateral bowed vocal cords, as can be caused by ageing, and may be useful to correct soft tissue defects in the vocal fold as a result of previous surgery, although the final voice expectations for these diagnoses should be quite guarded.

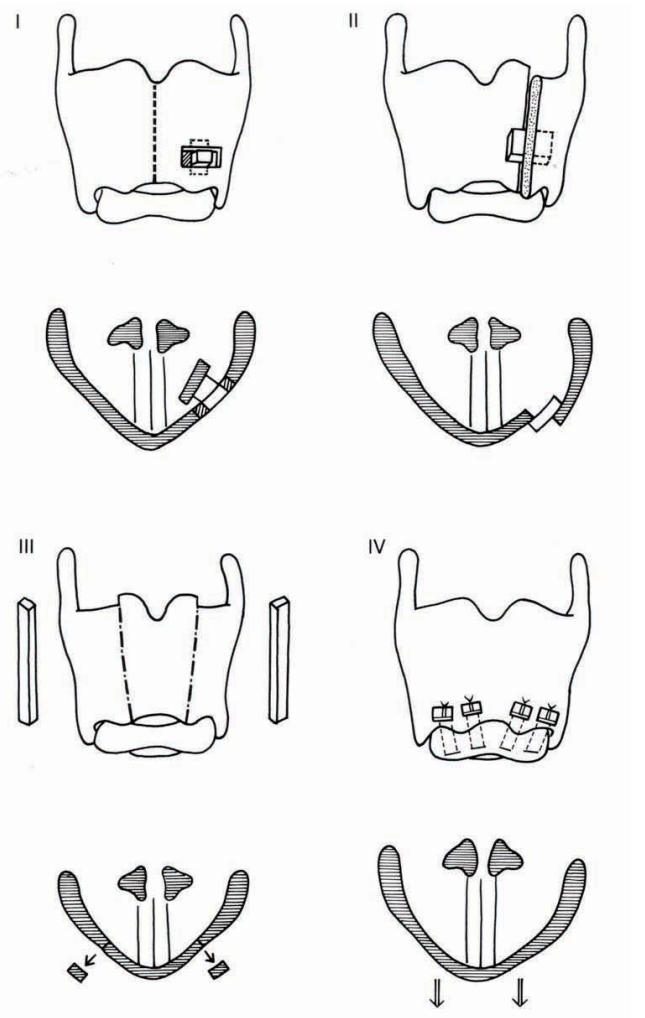

Figure 67.10 Types I, II, III and IV laryngeal framework thyroplasties, as described by Isshiki.

Techniques

Thyroplasty type 1 essentially involves medialization of the vocal cord by its inward displacement with an implant placed through a window in the thyroid cartilage (**Figure 67.11**). The comprehensive operating technique is well established[20] but some of the finer details are described here. In the original description the cartilage window was preserved but many now remove this island of cartilage, believing it can be displaced or absorbed, leading to later complications. There are specific instrument kits available for medialization laryngoplasty, which are not essential but can help to reduce the time of the procedure and ideally 30–40 minutes for a routine thyroplasty is adequate. Interestingly, one should preserve the outer perichondrium when using Gortex as this will need to be sewn back to close the defect (window) in the thyroid cartilage. It is still not certain whether a posterior glottic chink can be closed with a medialization thyroplasty alone and research on the anatomy of the cricoarytenoid joint suggests that when the paralyzed cord is on a different vertical plane to the normal one, then a medialization laryngoplasty is insufficient for full closure.

Isshiki[23] described an arytenoid adduction procedure for patients where there is a large posterior gap and the paralysed cord is at a different vertical level. Good results have been reported, both initially for a competent larynx and long term for voice production.[24] A modification of this technique is the arytenoid fixation and cricothyroid subluxation as described by Zeitels.[25] With an extended incision, the arytenoid cartilage is exposed, its attached muscles divided and the arytenoid cartilage is fixed in a midline position. Tension of the paralyzed cord is obtained by a suture between the inferior horn of the thyroid cartilage and the cricoid cartilage anteriorly (**Figure 67.12**). This is usually combined with a medialization thyroplasty and allows correct positioning of the arytenoid cartilage and gives tension and bulk to the paralyzed vocal cord. Although technically challenging, it is the author's personal choice for patients with a large posterior glottic chink.

Common problems with thyroplasty include inserting a prosthesis that is too small or inserting a prosthesis in the incorrect place. Revision thyroplasties have shown that many insert the prosthesis too high as they do not define the lower border of the thyroid cartilage (**Figure 67.11**). The vocal cords are found deep to the inferior half of the thyroid cartilage and inserting the prosthesis too high will displace the false cord and not allow glottic closure.

BEST CLINICAL PRACTICE

- ✓ Specific instrument kits are not essential; they may help to reduce operating time, but risk a one-size-fits-all surgery.
- ✓ Implants are made of silastic, hydroxyapatite or Gortex.
- ✓ Implant design varies to accommodate modifications in insertion technique and maximize some effects.
- ✓ Thyroplasty alone is unlikely to be able to close the posterior glottic chink.
- ✓ Poor results are usually due to the superior location of the thryoid window.

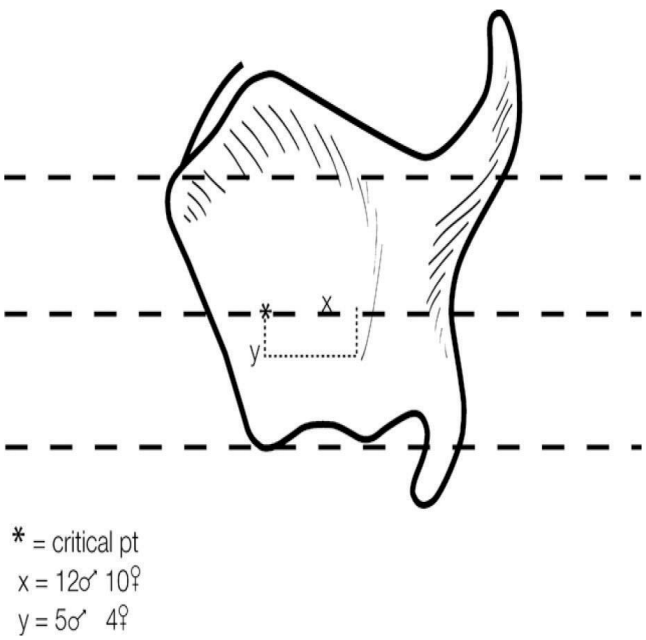

Figure 67.11 Dimensions (in mm) and location of window in thyroid cartilage.

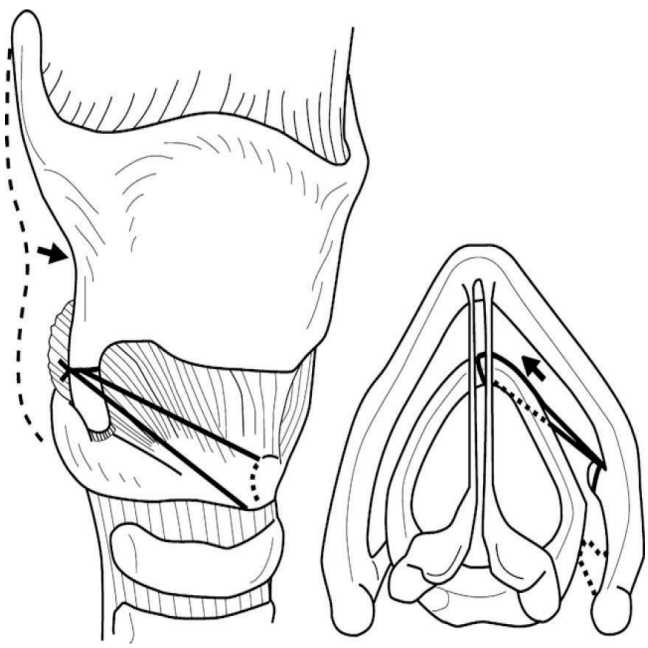

Figure 67.12 Suture gives tension to the paralyzed vocal cord with the arytenoid cartilage fixed medially.

REINNERVATION PROCEDURES

Recurrent laryngeal nerve anastomosis was initially described in 1909 by Horsley[26] and further work suggested that this was a successful technique but with no objective evidence to support the conclusions. Recently, Crumley[27] has popularized the technique of ansa cervicalis to recurrent laryngeal nerve anastomosis.

Neuromuscular physiology

The recurrent laryngeal nerve is a mixed nerve containing afferent, sympathetic, parasympathetic and 500–1000 motor axons in an adductor to abductor ratio of 5 : 1. The ansa cervicalis, however, contains efferent fibres from the first three cervical nerves to innervate the strap muscles. Whereas the intrinsic laryngeal muscles are controlled to contract at specific times, the strap muscles have not been shown to have any phasic action in the primate. Reinnervated muscle takes on the characteristics of its supplying nerve, and the selection of the donor nerve should take into account the muscle fibre composition of the muscle to be reinnervated.

Muscle fibres can be divided into specific types based on the histochemical and contractile properties. There are three basic groups:

1. **Type 1:** slow contractile period and aerobic metabolism
2. **Type 2B:** fast contractile period and anaerobic metabolism
3. **Type 2A:** intermediate contractile period and both aerobic and anaerobic metabolism.

Muscles that produce low tension over a sustained time period will have a high concentration of type 1 muscle fibres. A high concentration of type 2 fibres will be seen in muscles that contract rapidly generating high tension over a short time. The intrinsic muscles of the larynx differ in their constitution of muscle fibres but the thyroarytenoid muscle (part of which is the vocalis muscle of the vocal fold) has a fast contraction time (14 milliseconds) and < 36% type 1 muscle fibres. The strap muscles, however, have a higher percentage of type 1 muscle fibres (66%) and a contraction time of 50 microseconds. The distribution of neuromuscular endplates in each of the intrinsic laryngeal muscles and the strap muscles are also different, with a diffuse pattern in the thyroarytenoid but a typical skeletal muscle distribution in the strap muscles where they form a narrow band at the midpoint. This gross difference in the histochemical and contractile properties of these muscle groups and their nerve supply makes them poor recipients and donors for nerve transfer. It is proposed that the unfavourable synkinesis that occurs in

TABLE 67.1 Comparison of procedures currently used for the rehabilitation of a patient with unilateral vocal fold paralysis

Procedure	Time taken (minutes)	Results	Anaesthetic	Demand on technical skill	Complications
Fat injection	10–30	Immediate but 30–50% and in 1/12 good voice results	Local/general	Moderate	Under-injection
Glycerine injection	10–30	Immediate	Local/general	Moderate	Over-injection
					Airway compromise
					Under-injection
					Over-injection
Fat injection	10–30	Immediate but 30–50% and in 1/12 good voice results	Local/general	Moderate	Airway compromise
Collagen injection	10–30	Immediate	Local/general	High	Under-injection
					Over-injection
Glycerine injection	10–30	Immediate	Local/general	Moderate	Airway compromise
Silicone injection	10–30	Immediate	Local/general	High	Under-injection
					Over-injection
Collagen injection	10–30	Immediate	Local/general	High	Airway compromise
Laryngeal framework surgery	35–75	Immediate	Local/general	Moderate	Wound infection
					Haematoma
Silicone injection	10–30	Immediate	Local/general	High	Airway compromise
					Mucosal perforation
					Dislodgement and/or extrusion
Reinnervation	60–120	2–3 months (+ Gelfoam/Glycerine injection)	General	Most	Wound infection
					Haematoma
					Loss of abnormal synkinetic tone (Flaccid fold)

a damaged recurrent laryngeal nerve with mixed partial axonal regrowth is replaced by a more favourable synkinesis from the ansa cervicalis.

Muscle nerve pedicle reinnervation has also been described using a block of omohyoid with its branch from the ansa cervicalis, although some surgeons are now combining neural anastomosis with laryngeal framework surgery as it appears that neural anastomosis alone does not give a good result in a lateralized cord. In the author's opinion, there is currently no convincing clinical or scientific evidence that the reinnervation techniques give better or equal results to either injection, medialization or laryngeal framework surgery in the management of a unilateral vocal cord paralysis. **Table 67.1** shows the advantages and disadvantages of the most common procedures currently used for the rehabilitation of a patient with a unilateral vocal cord paralysis.

FUTURE RESEARCH

Phonosurgery would benefit from:

- ➤ improved methods of measuring voice (i.e. objective, subjective, patient based) for meaningful comparison
- ➤ reliable surgical interventions for vocal fold scar
- ➤ Clinical trial for the establishment of safe adjuvant treatment for successful management of respiratory papillomatosis.

KEY POINTS

- The underlying etiology of the vocal abnormality must be established before any treatment can be offered.
- Complete assessment with videostroboscopy and voice measurements pre- and post-surgery are desirable.
- Knowledge of the anatomy and microstructure of the vocal cords and location of lesion is essential.
- Selection of laryngoscopes, micro-instruments and operative lasers are required before phonosurgery can be performed.
- Vocal fold nodules should rarely, if ever, require phonosurgery.
- Materials such as calcium hydroxyappetitie have replaced Teflon for vocal fold injection laryngoplasty.
- Laryngeal framework surgery can be performed under local anaesthesia for intra-operative auditory feedback.

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CHAPTER 68

MOVEMENT DISORDERS OF THE LARYNX

Declan Costello and John S. Rubin

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SEARCH STRATEGY

Data in this chapter may be updated by a PubMed search using the keywords: dysphonia, spasmodic dysphonia, Parkinson's disease and vocal tremor.

INTRODUCTION

The larynx is subject to highly complex neurological control to fulfil its roles in phonation, deglutition and respiration. Dysfunction of the movement of the larynx may reflect a wider neurological condition or may be an isolated disorder of the vocal tract.

In broad terms, disorders of movement of the larynx can be thought of as either hypofunctional or hyperfunctional. Further conditions may be related to poor coordination or stability of the voice.

HYPOFUNCTIONAL CONDITIONS

Parkinson's disease

Parkinsonism is a term referring to a group of conditions including idiopathic Parkinson's disease (PD), Parkinson's plus syndromes and secondary Parkinson's.

Idiopathic PD accounts for around 80% of cases of Parkinsonism; it is a nigrostriatal disorder characterized by a deficiency of dopamine. Generalized rigidity is seen, along with bradykinesia (slowness of movement). These two aspects are collectively described as hypokinesia. Tremor (typically a 'pill-rolling' tremor) is a very common feature. PD is a relatively common neurological disorder, with a prevalence of 1 per 1000 of the population, rising to around 1 per 100 in the over-60 age group.[1]

Although PD is usually thought of as a condition of older age, it can also affect younger patients.

The voice in patients with PD is typically described as 'monotone' and reduced in volume. These features are a consequence of reduced activation of the thyroarytenoid muscle.[2] Examination of the larynx will characteristically show bowing of the vocal folds, resulting in a quiet and breathy vocal quality. This weakness of voice is accompanied by dysarthria (poor articulation).

MANAGEMENT OF PD

Systemic treatment with dopaminergic agents (levodopa, l-dopa) can achieve significant improvements in the peripheral symptoms; however, these improvements are not always reflected in changes in the voice.[3] In recent years, the application of the Lee Silverman Voice Treatment (LSVT) has resulted in dramatic improvements for many patients. The LSVT mode of management requires a specific programme of intensive sessions of daily therapy over a one-month period.[4]

PARKINSON'S PLUS SYNDROMES

Progressive supranuclear palsy

Progressive supranuclear palsy (PSP) is a neurological condition that results from accumulations of tau protein in the basal ganglia, brainstem and cerebral cortex. Initial symptoms include loss of balance and bradykinesia.

Ocular symptoms such as poor control of eye movements are seen. The speech and laryngeal manifestations in patients with PSP include dysarthria and monotone voice. Treatment is essentially palliative, with l-dopa sometimes providing some control of symptoms.

Multiple-system atrophy

Multiple system atrophy (MSA) is a degenerative disease in which there is cell loss in specific areas of the brain. Autonomic failure is a common feature, and in these cases, the condition is referred to as Shy-Drager syndrome. The laryngeal manifestations may include bilateral vocal fold paresis or paralysis. The voice may exhibit hypo- or hyper-functional features, being either breathy and weak or loud and strained.

Motor neurone disease

Motor neurone disease (MND) refers to a group of disorders that includes amyotrophic lateral sclerosis (ALS), progressive bulbar palsy (PBP), progressive muscular atrophy (PMA), and primary lateral sclerosis (PLS). Of these, ALS is the most common. MND is characterized by progressive degeneration of the motor cells of the brain and spinal cord. Both lower motor neurone (LMN) and upper motor neurone (UMN) dysfunction occurs, usually with LMN signs predominating. The progression of the disease is usually rapid and life expectancy is typically 2 to 5 years from diagnosis.

The usual presentation (in 80% of cases) is in the limbs, with limb weakness, fasciculations and brisk reflexes. However, 20% of cases will present with bulbar signs and symptoms; these include dysarthria (as a result of limitation of tongue movement), tongue fasciculation, dysphagia and nasal regurgitation. Voice changes can comprise a 'wet' sounding voice as a result of pooling of secretions in the larynx, along with a harsh and/or breathy voice quality, and often vocal tremor. Hypernasality can result from poor velopharyngeal function.

Swallowing is generally affected as well as voice, with aspiration pneumonia a possibility. Not infrequently, adjunctive management of swallow (with a gastrostomy) as well as of airway (with tracheostomy) are required.[5]

Myasthenia gravis

Myasthenia gravis (MG) is an autoimmune disorder in which antibodies to the postsynaptic acetylcholine muscle receptors prevent neuromuscular transmission. This results in progressive muscle weakness and fatigability. Small muscles are usually the first to be affected, most frequently those around the eye. That said, up to 20% of patients initially present with voice changes – most often vocal fatigue; this is frequently with a negative acetylcholine receptor antibody titre.[6] Other laryngological changes include stridor and voice weakness. More broadly, the voice may sound hypernasal and the patient may be dysarthric. A misdiagnosis of superior laryngeal nerve palsy and/or bilateral vocal fold paresis may delay the formal diagnosis of MG.

Because fatigability is a key finding in MG, laryngeal examination should include asking the patient to perform repeated vocal tasks.[7] Treatment of MG centres on the administration of anticholinesterase drugs (pyridostigmine); in some cases steroids are required and occasionally thymectomy is undertaken.

Vocal fold paralysis

Paralysis of one or both vocal folds may result from one of a wide number of neurological conditions – many of these are described above. A detailed description of vocal fold paralysis is outlined in Chapter 78, Paralysis of the larynx.

HYPERFUNCTIONAL CONDITIONS

Pseudobulbar palsy

A UMN lesion in the corticobulbar pathway may cause difficulty chewing, manipulating a food bolus in the oral cavity, swallowing, and dysarthria. The most frequent cause is cerebrovascular accident, but other causes may include demyelination (multiple sclerosis), PSP, ALS, PD, MSA and malignancy. The voice may exhibit a strained and strangled quality, and running speech shows dysfluency.

Huntington's disease

Huntington's disease is inherited in an autosomal dominant pattern. It is a neurodegenerative disease in which patients exhibit involuntary muscle movements (chorea), as well as cognitive and psychiatric problems.

Poor coordination of muscle movements is also seen in the larynx, and results in a wide variety of vocal changes: poor control of pitch and volume may occur, along with a strained voice quality or complete voice breaks.[8, 9]

Spasmodic dysphonia

Of the conditions described above, few are amenable to specific treatment that can improve the vocal quality, and in most cases, only supportive treatment can be offered. In contrast, the symptoms of spasmodic dysphonia (SD) are readily controlled with injections of botulinum toxin, combined with voice therapy to eliminate hyperfunction.[34]

SD is a voice disorder arising from a focal dystonia involving certain laryngeal muscles[10–12] but reflecting central motor processing issues/abnormalities.[13] It is only present during certain specific speech vocal tasks, and can be overridden by vegetative phenomena such as laughing or by chanting or singing. There is a background of normal speech overlain by vocal spasms that are not under voluntary control. This leads to a typical strained and strangled speech pattern[14, 15] that was recognized by MacKenzie more than a century ago.[16]

SPASMODIC DYSPHONIA: AETIOLOGY AND INCIDENCE

Early theories suggested that SD was a psychoneurosis.[17, 18] It was then determined to be of neurological origin and to represent a focal dystonia.[9, 19] Recent functional MRI (fMRI) studies have failed to identify any specific structural defect. In most instances the aetiology of SD is unknown/idiopathic although not uncommonly the patient will relate onset to a specific event such as a 'flu-like syndrome or an emotionally traumatic event.

At the time of writing this chapter, at least 13 genes or chromosomal locations have been associated to dystonias and several to voice disturbances on case-report basis. Recently, the DYT6 dystonia (a primary, early-onset torsion dystonia) has been found to be caused by mutations in the THAP1 gene (thanatos-associated protein domain containing apoptosis-associated protein 1).[20–22] Further studies have identified THAP1 mutations in certain dystonias (both generalized and focal), and this has included cases with early involvement of the larynx.[23] Involvement is limited, however, and in 160 patients with SD screened, only 1% had THAP1 mutations.[23]

In general, approximately 8% of patients have a family history of dystonia,[20, 24] but this is less commonly the case with SD. Blitzer[25] highlights that most cases of SD are sporadic, although Schweinfurth et al. in their case series noted a 20% association with other forms of focal dystonias.[14, 26]

Estimates of incidence vary, with one being given at 1 per 100 000.[27] It is unclear if SD is a relatively rare disorder or whether failure of recognition of the condition results in a low pick-up rate. There are approximately 30 000 to 50 000 people in North America affected. Because of the difficulty securing the diagnosis, there is usually a long interval between onset of symptoms and diagnosis; in our experience, this is approximately 2–3 years (Costello and Rubin, personal observations). SD is more prevalent in females than in males and the average age of onset is 40 years.

Ludlow summarizes that the current view points to focal dystonia is due to a combination of genetic predisposition interacting with acquired factors later in life, for example head injury, drug exposure or peripheral injury.[15]

SOCIAL IMPLICATIONS

SD has significant social implications and impacts on the patient's quality of life. Due to the phonation breaks and strangled quality of the voice (and the fact that symptoms are worse when stressed or when speaking over the phone), individuals affected may become socially isolated. There is no question that it affects communication and causes major social disruption in the lives of sufferers. Izdebski et al. have noted that SD affects job performance in 77–93% of affected individuals and that 26–37% need to change job or be reclassified within the work setting.[28–31]

CLINICAL FEATURES

SD is a task-specific dystonia: the spasm only occurs on phonation. On endoscopy at rest, the larynx appears normal, but on phonation, spasm of the laryngeal musculature is seen and heard. It is also typically worsened by use of the telephone or in times of heightened anxiety, for example when meeting people for the first time. Many patients report that alcohol intake ameliorates symptoms of SD.

The airway is not compromised in SD – adduction occurs only on phonation and never during respiration.

SPASMODIC DYSPHONIA: TYPES

SD tends to be differentiated by symptoms into **adductor**, **abductor** and **mixed** types.

Adductor SD

Adductor SD is by far the commonest type, affecting approximately 90% of patients with SD.[32] The characteristic adductor spasm results in a strangled and staccato voice. This can easily be mistaken for muscle tension dysphonia, and is frequently treated as such for some time before SD is diagnosed.

It is characterized by phonation breaks associated with vowels, in particular words ending with a vowel and being followed on by a word starting with a vowel (for example 'we – eat') and words with two vowels in tandem (for example, eighty-year – eels). The vowels /i/ ('ee') and /a/ ('ah') are particularly problematic. Interestingly, patients may often produce a relatively normal phonation on a continuous vowel sound.

Hyperfunctional voice and psychogenic voice disorder may be confused with SD. Hyperfunctional voices tend to have voice hallmarks of prolonged, constant strained voice but with no phonation breaks. Spastic UMN conditions may also be misdiagnosed as SD.

Abductor SD

Abductor SD is far less common. In our practice we have identified it as the predominant presentation in under 10% of individuals presenting with voice dystonias. Individuals with abductor SD have particular difficulty with voice onset after voiceless consonants at the beginnings of words or phrases (words starting with /w/, /b/, /s/, /t/, /p/, /f/, etc.), often leading to problems with vocal fold closure for the following sound. Typical examples given include phrases such as 'who has hidden Harry's hat?'. Attempts to pronounce such sounds lead to voiceless voice breaks.

Disorders that may be confused with abductor SD include psychogenic voice disorders such as whisper dysphonia and neurologic disorders, in particular forms of Parkinsonism.

DIAGNOSIS

The diagnosis of SD is made on clinical grounds, and usually solely by the listening skills of an experienced clinician. Both in adductor and abductor SD, it is often the case that patients have seen numerous clinicians before a diagnosis of SD is reached. To the untrained ear, the voice may sound so unusual that patients are sent for speech

therapy, psychotherapy and alternative therapies to treat what is thought to be a psychogenic phenomenon.

Electromyography (EMG) will demonstrate bursts of involuntary spasms of electrical activity overlaid on normal interference pattern.[33] In adductor SD, increased thyroarytenoid activity is observed during these bursts.[33] That said, EMG does not really improve the diagnosis made with the ear, but instead serves to confirm it, except in particularly difficult diagnostic circumstances (Rubin, personal observation).

Assessment of SD requires evaluation by a multidisciplinary team. Core members include the speech-language therapist, otolaryngologist, neurologist and neurophysiologist. It is most helpful to have a good relationship with psychologist and psychiatrist as well. A careful case history, emphasizing the psychosocial aspects, is fundamental to diagnosis as well as successful management.

Nasendoscopic inspection and recording with playback to the patient is the gold standard. It is interesting to note that the insertion of the nasendoscope may temporarily diminish the spasm. This unexpected finding gives weight to the hypothesis that SD may be primarily a disorder of sensory input: the altered afferent input from the pharynx and larynx during endoscopy appears in some way to modulate the efferent motor signals, and can reduce the amount of spasm. Assessment by the speech-language therapist with a trial of voice therapy generally occurs, and all patients are referred for baseline neurological evaluation.

Speech-language therapists have a crucial contribution to differential diagnosis. Their role includes perceptual and instrumental assessment that are critical to measurement of baseline status and outcome, patient counselling in all cases and voice therapy in some cases; therapeutic techniques, when combined with botulinum toxin injections, can improve outcomes.[34]

The voice assessment includes repetition of sentences loaded with voiced segments and vowels, as this will provoke (worsen) symptoms (i.e. more strain, voice breaks). In adductor SD, sentences loaded with voiceless segments will decrease symptoms (i.e. improved performance, less strain and fewer voice breaks) whilst voiced consonants will make the voice worse (**Box 68.1**).

Other task-specific tests to detect adductor SD include:

1. Sentences with all voiced consonants to provoke more symptoms: 'Early one morning a man and a woman were ambling along a one-mile lane running near rainy island avenue.'[35]
2. Sentences with mostly voiceless consonants to provoke fewer symptoms (i.e. better voice with this phonetic context): 'He saw half a shape mystically cross fifty or sixty steps in front of his sister Kathy's house.'

BOX 68.1 Voiced (voice 'on') versus voiceless (voice 'off')

Voiced consonants	Voiceless consonants
Stops /b/, /d/, /g/	Stops /p/, /t/, /k/
Fricatives /v/, /z/,/ zh/	Fricatives /f/, /s/, /sh/, /h/
Affricates /dz/	Affricates /ch/
Glides & liquids /w/, / r/, /l/, /j/	

BOX 68.2 Laryngoscopy protocol

Quiet respiration
Prolonged /i/; /a/
Repetitive /i/ /i/ /i/
/si/ /si/ /si/
/mi/ /mi/ /mi
/isi/ /isi/ /isi/
We eat eel every day
She speaks pleasingly
We mow the lawn all year
Peter will keep at the peak
The puppy bit the tape
Harry has a hat; his hat is on his head
When he comes home we'll feed him
Taxi, Taxi, Taxi
Tell me about your voice problem or how did you get here today
Alternating high and low pitch phonations

In the clinic, two vocal tasks are particularly helpful: adductor SD is commonly more detected when the patient counts upwards from the number 80 ('80–81–82–83…'). For abductor SD, counting from 50 ('50–51–52–53…') will exacerbate the spasm. These tasks may be used prior to and then during nasendoscopy (**Box 68.2**).

Tremor

Vocal tremor can occur on its own or with SD. It is said to be present in approximately one-third of individuals with SD.[36] In tremor, regularly spaced voice breaks are noted particularly on prolonged vowel /a/ or /I/. The modulation is at between 3 and 5 Hz. Tremor affects women most commonly, especially in middle age. Often, tremor is more evident in the chest voice, rather than the head voice.

Familial forms of tremor may lead to vocal manifestations in the absence of laryngeal dystonia. Essential tremor, the most common form of movement disorder, has a prevalence of approximately 4% of individuals aged 40 and older, increasing with age. Whilst it affects all age groups, its incidence increases with age. No genes have been identified yet but inheritance patterns are said to be most consistent with autosomal dominance. Hands and feet are most commonly affected, but the voice is affected in 4–20% of cases. On PET scanning, in certain instances the olivo-cerebellar tracts have been noted to be abnormal, with increased cerebellar activity even at rest.

TREATMENT OF SPASMODIC DYSPHONIA

As no definitive cause for SD has been established, the treatment centres on controlling symptoms.

Speech therapy

There is little role for speech therapy in the management of SD. In some cases, therapy may help to ameliorate some of the compensatory tension patterns that develop as a consequence of the dystonia, but therapy alone is never curative. This is borne out by recent research[37] demonstrating no additional improvement in voice outcomes with the inclusion of therapy as well as botulinum toxin injection.[34]

One form of voice therapy, 'inhalational speaking', has been espoused by Shulman to allow individuals with severe SD to phonate.[38] We have anecdotally noted several of our patients to attempt phonation in this manner (Rubin, personal observation 2011).

However, the role of the speech therapist in the diagnosis of SD is essential, as therapeutic techniques can often help to differentiate between SD and muscle tension dysphonia. They also have a critical role in monitoring voice quality and managing side effects.

Medical therapy

In cases of isolated SD, there is no role for systemic medical therapy. However, in cases of SD associated with other dystonias (facial dystonia, for example), low-dose benzodiazepines may be useful.

Botulinum toxin

The mainstay of treatment of SD is repeated botulinum toxin injections.[39–42] In clinical practice in the UK, most clinicians use botulinum toxin type A.

Botulinum toxin is a neurotoxin produced by the gram-positive anaerobic bacterium *Clostridium botulinum*. There are seven types that are structurally similar but antigenically and serologically distinct. The established drug names have changed over time to reinforce the differences and prevent medication errors. The current products include:

- OnabotulinumtoxinA (Botox, Botox Cosmetic). Botox is approved for cervical dystonia, severe axillary hyperhydrosis, strabismus and blepharospasm. Botox Cosmetic is approved for moderate-severe glabellar lines.
- AbobotulinumtoxinA (Dysport), approved for cervical dystonia, moderate-severe glabellar lines.
- IncobutulinumtoxinA (Xeomin) approved for cervical dystonia and blepharospasm.
- RimabotulinumtoxinB (Myobloc) approved for cervical dystonia.

The molecule is synthesized as a single chain (150 kD) and then cleaved to form the dichain molecule with a disulfide bridge.[43, 44] Botulinum toxin acts by binding presynaptically to high-affinity recognition sites on cholinergic nerve terminals, causing a neuromuscular blocking effect by decreasing release of acetylcholine. Slow recovery occurs by proximal sprouting of axons and muscle reinnervation by the formation of a new neurotransmitter junction, with ultimate regeneration of the original neuromuscular junction.[45]

ADDUCTOR SD – BOTULINUM TOXIN INJECTIONS

For patients with adductor SD, the injections of the thyroarytenoid muscle with botulinum toxin may be performed permucosally (under local or general anaesthetic) or, more commonly, transcutaneously.

The transcutaneous injection technique approaches the thyroarytenoid muscle through the cricothyroid membrane. After sterilizing the skin, the needle is advanced in the midline through the cricothyroid membrane. Care must be taken not to enter the airway: this will cause the patient to cough. Having entered the skin and passed through the cricothyroid membrane, the needle is angled 15 degrees cranially and 30 degrees laterally and then advanced into the body of the thyroarytenoid muscle. No local anaesthetic is required as the injection needle is of a very small calibre (generally 26G) (see **Figures 68.1**, **68.2** and **68.3**).

Many clinicians use electromyographic (EMG) monitoring to ensure that the tip of the injection needle is appropriately placed in the thyroarytenoid muscle. The EMG needle electrode is a fine-bore needle with an insulated shaft and an exposed electrode tip at the point. The circuit is completed with a wire that is connected to an EMG. The use of EMG can confirm that the needle tip is in *a* muscle, but will not help the clinician to know *which* muscle. When the needle tip is thought to be in the muscle, the patient is asked to phonate (/i/) – this causes a characteristic burst of activity on the EMG monitor, and the botulinum toxin can be rapidly delivered into the muscle.

In general, patients will receive a low dose of botulinum toxin (between 3 and 10 units of dysport (equal approximately to between 1 and 3 units of botox)) into one or both thyroarytenoid muscles. In practice, a newly diagnosed patient will usually receive a small dose of botulinum toxin into one or other vocal fold. The dose is then titrated upwards (or downwards) according to the patient's response. The frequency of dosing is variable: in some patients, injections are only required every

TABLE 68.1 Commonly used preparations of Botulinum toxin A and their relative properties

Name of preparation	Botox	Dysport	Xeomin
Manufacturer	Allergan	Ipsen	Merz
Dose equivalence	1 unit is equivalent to	3 units are equivalent to	0.75 units
Storage	Refrigerated	Refrigerated	Room temperature

Figure 68.1 Setup for laryngeal injection of Botulinum toxin, with EMG machine.

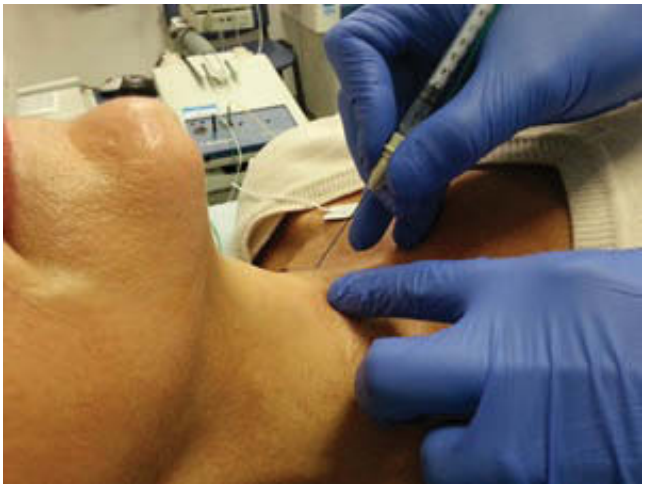

Figure 68.2 Note that the skin is entered at the cricothyroid membrane.

Figure 68.3 The patient's neck is extended by placing a pillow under the shoulders.

6 months; in others, they can be required every 6 weeks. In the 7 days after an injection, the patient can expect their voice to be a little weak and breathy. During this time, they may also experience problems with aspiration of liquids. Following this, the voice will reach a steady state, and should reach its maximal benefit 2–3 weeks after the injection.

On the whole, a higher dose will have a longer duration of effect. On the other hand, a higher dose will also give rise to more side effects (such as breathy voice and aspiration of liquids). Every patient requires a subtly different timing and dosing of injections and will have personal preferences; for example, a retired patient who lives a long distance from the clinic may be happy to have a higher dose (and accept the initial side effects) if (s)he only has to attend every 6 months. Conversely, a working professional may be willing to attend the clinic every 6 weeks for a low dose in order not to have a period of vocal weakness.

In a questionnaire survey of American laryngologists injecting botulinum into the larynx, most reported that they used EMG to guide needle placement; more perform bilateral injections than unilateral; almost all are guided by their patients' wishes and complications from previous injections as to their subsequent injection and dosage; and most inject 3–4 times per year.[46]

We performed a subjective patient-reported questionnaire looking at relative success rate and complications (length of breathiness, swallowing issues, cough) in a group of our patients with adductor SD. We found 94% 'success' rate from the previous injection, mean dose (Dysport) in our unilateral injections of 3.6 iU, mean dose bilateral of 6.6 iU. In this group, we did not find significant differences in terms of length of breathiness, cough or dysphagia between low dose unilateral or bilateral injection.[47]

ABDUCTOR SD – BOTULINUM TOXIN INJECTIONS

Accessing the posterior cricoarytenoid (PCA) muscle for injection of botulinum toxin is more difficult; its location at the posterior aspect of the larynx makes injection more technically challenging. It may be approached transcutaneously by manually rotating the larynx into a position where the posterior cricoid ring can be accessed. This is a deep injection in the neck, and often requires local anaesthetic. If the PCA is injected transcutaneously, EMG guidance is essential; the muscle can be difficult to locate, and EMG confirmation (by asking the patient to abduct the vocal folds with a forced sniff) is required to confirm needle placement.

Some clinicians prefer to perform PCA injections under general anaesthetic. This is performed by lifting the larynx forwards with a laryngoscope and injecting behind the cricoid ring into the PCA muscle. Care must be taken to direct the injection laterally; erroneous injection of both PCA muscles might result in complete failure of the patient to be able to abduct *both* vocal folds, and consequent airway compromise.

Botulinum toxin injections for abductor SD appear to be less effective than for adductor SD. A larger dose is usually required to achieve adequate results.

SURGERY

Recurrent laryngeal nerve section/crush

In 1976, Dedo first described a technique of unilateral recurrent laryngeal nerve (RLN) sectioning for adductor SD.[48–50] Initial results were promising, but further follow-up[51] demonstrated that longer-term results were not maintained.

Recurrent laryngeal nerve selective denervation and reinnervation

There are two significant problems with nerve section/crush: first, the muscle may be prone to atrophy; and second, there is a likelihood of reinnervation by the cut end of the RLN. Berke et al. have postulated that selectively denervating the thyroarytenoid and lateral cricoarytenoid muscles, followed by providing tone to the muscles with an ansa cervicalis anastomosis, might preserve muscle tone.[52, 53] The results appear impressive, with 82% of patients reporting that they would recommend the surgery to others.[54]

Thyroarytenoid myotomy

A method of causing thyroarytenoid inactivity has been proposed by coagulating the muscle with a laser. In a small series, this has proven to be a promising treatment option.[55, 56]

Type 2 thyroplasty

Isshiki has proposed a type 2 thyroplasty as treatment for adductor SD.[57, 58] In this procedure, the anterior larynx is approached through a neck incision. The thyroid cartilage is divided in the midline (as for a laryngotomy), taking care not to enter the airway. A shim (of titanium in Isshiki's description) is inserted to produce a separation of the anterior vocal folds at the anterior commissure. This is performed under local anaesthetic, allowing the patient to talk, so that the correct size of shim can be ascertained intra-operatively. In this relatively large series (41 patients), the results are very promising.

KEY POINTS

- Systemic neurological conditions can have profound effects on the voice, airway and swallowing.
- Multidisciplinary working is critical, including neurologists, laryngologists, speech therapists (with specific skills in treating neurologically disordered patients) and radiologists.
- Many neurological conditions are best treated with voice therapy and supportive care.
- Spasmodic dysphonia is a rare focal dystonia of the larynx; it is frequently misdiagnosed but is readily amenable to treatment with injections of botulinum toxin.

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CHAPTER 69

ACUTE INFECTIONS OF THE LARYNX

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SEARCH STRATEGY

Data in this chapter is based on a Pubmed and Ovid (Medline) search of the English language literature. The MeSH key words used were laryngitis, epiglottitis, croup, laryngotracheobronchitis, pertussis and other search terms used were supraglottitis, laryngeal infections, upper airway infections. The clinical recommendations are predominantly group C.

INTRODUCTION

Acute infections of the larynx are not unusual and are most commonly associated with an upper respiratory tract infection that is usually of viral origin. Therefore, these conditions are mostly managed in the primary care setting. However, there are specific types of infections of the larynx that require specialized care and it is therefore essential for the practising otorhinolaryngologist to be familiar with these conditions.

Furthermore, although the majority of acute laryngeal infections are self-limiting and resolve with supportive care, in a small number of cases an acute infection can progress rapidly into a life-threatening condition requiring urgent expert care in a hospital setting. This will often require input from an experienced team of clinicians, which may include an emergency medicine physician, otorhinolaryngologist, anaesthetist, paediatrician and microbiologist.

In this chapter, we provide an overview of the types of acute laryngeal infections and management strategies for dealing with these conditions.

CLINICAL FEATURES

The term laryngitis refers to inflammation of the tissues of the larynx. In acute forms the onset is usually abrupt. The general symptoms and signs of acute laryngeal infection are listed in **Table 69.1**.

Stridor is a serious symptom as it is associated with significant airway narrowing. It is more commonly seen in children and such cases should be managed jointly with a paediatrician in a hospital setting. Narrowing at the supraglottis or glottis is typically associated with inspiratory stridor. Narrowing below the level of the glottis may also present with inspiratory stridor but typically will be biphasic in nature.

Examination of children with stridor should be done by an experienced clinician with care taken not to cause any additional distress to the child. In adults, a flexible laryngoscopy is required for direct visualization of the larynx in most cases. This allows an assessment of

TABLE 69.1 Signs and symptoms of acute laryngeal infection

Symtoms	Signs
Dysphonia	Tender laryngeal framework
Dyspnoea	Stridor
Sore throat	Cervical lymphadenopathy
Odynophagia	Pharyngitis
Referred otalgia	Pooling of saliva

the vocal cords themselves, the supraglottis and an overall clinical assessment of the patency of the laryngeal airway.

ACUTE LARYNGITIS

Acute laryngitis is a common inflammatory clinical condition of the glottis and supraglottis. It is most commonly due to a virus associated with an upper respiratory tract infection. It may also occur secondary to infections of the upper and lower respiratory tract such as tonsillitis or chest infections.

The majority of cases of acute laryngitis are self-limiting and resolve within a couple of weeks. Patients typically present with a hoarse voice associated with symptoms of a common cold. In some cases, there may be a superadded bacterial infection that may lead to a more severe type of laryngitis. Fungal infections of the larynx are dealt with in 'Mycotic laryngitis' below.

Treatment initially includes vocal hygiene measures including voice rest, analgesics/anti-inflammatory medications, avoidance of irritants (e.g. smoking and alcohol) and maintaining good hydration of the larynx. Steam inhalation has been used although most of the reports are in children with croup and there is no good evidence of benefit.[1]

The role of antibiotics in cases of acute laryngitis should be reserved for cases where there is clinical suspicion of bacterial infection. Typically, these patients may have persistent and more severe laryngitis or other associated infections of the upper or lower respiratory tract. In general, antibiotics have little role in the treatment of the majority of cases of acute laryngitis,[2, 3] although there is some evidence that erythromycin may reduce voice disturbance in the first week and therefore may be considered in patients who are professional voice users.[4] The choice of antibiotic depends on any associated infections but penicillin has been reported as being ineffective[5] and macrolides (e.g. erythromycin or clarithromycin) have been shown to be effective, which may be a reflection of infection with *Moraxella catarrhalis*.[6]

There have been recent case reports of methicillin-resistant *Staphylococcus aureus* laryngitis[7, 8] and this should be considered in cases not responding to first-line antibiotics. Diagnosis will be made by microlaryngoscopy and cultures, which should be considered in cases that are not responding to first-line treatment.

Patients with stridor generally should be admitted to hospital and intravenous antibiotics, nebulized adrenaline and steroids considered. It is important to liaise with an experienced anaesthetist and the patient should be observed in an appropriate clinical setting such as a high dependency unit. If there is airway compromise that is deemed severe enough then early intubation and ventilation should be considered until the airway inflammation has improved. Tracheostomy is rarely indicated.

Patients with persistent hoarseness lasting for more than a few weeks should be reviewed in a specialized voice clinic along with a speech therapist. The pathogenesis of laryngeal inflammation can be multifactorial and factors in addition to the viral or bacterial infection, such as smoking, allergy, rhinosinusitis, voice abuse and laryngopharyngeal reflux, should also be managed appropriately.[9] If doubt as to the diagnosis persists then formal microlaryngoscopy should be considered.

EPIGLOTTITIS (SUPRAGLOTTITIS)

Epiglottitis is an acute infection of the supraglottis characterized by inflammation of the supraglottic structures. It is usually due to a bacterial infection and should be considered to be an emergency condition due to the potential rapid and fatal airway obstruction. The incidence of epiglottitis is 1–2/100 000.[10, 11]

Historically the most common causative organism was *Haemophilus influenza* type b (Hib), which accounted for almost 90% of cases.[8] The incidence of epiglottitis (particularly in children) has decreased significantly as a result of the *Haemophilus influenza* type b vaccination, which was introduced in the UK in 1985 to prevent childhood meningitis.[12, 13] However, this has led to the emergence of other causative organisms (e.g. *beta haemolytic Streptococcus*, *Streptococcus pneumoniae*, *Streptococcus milleri*, *Staphylococcus aureus*, *Escherichia coli*, *Klebsiella pneumoniae*, *Neisseria* spp.) and there has been an increase in the incidence of adult epiglottitis that is not related to *Haemophilus influenzae* infection.[11, 14, 15] Fewer than 20% of cases of adult epiglottitis are due to *Haemophilus influenzae*.[15] *Candida albicans* is an important cause to consider in immunocompromised patients.[14, 16]

Historically the condition was more common in children than in adults and it is important to recognize that the condition presents a somewhat different clinical picture between the two age groups. In a retrospective dataset study from the United States, Shah et al. found that the typical patient admitted with epiglottitis is a 40-year-old male and that the majority of mortalities from epiglottitis were in the adult population.[17]

The clinical features vary somewhat between children and adults. In adults, the main complaint is of a painful throat with associated odynophagia.[10, 11, 14] Dyspnoea, fever and drooling may also be seen but are not always present.[10, 12, 18] As the calibre of the airway is larger in adults than children, features of upper airway obstruction may not always be present. A significant proportion of adults presenting with epiglottitis will have comorbid conditions such as diabetes, hypertension, cardiac and respiratory conditions, complications of which have an associated mortality in patients with epiglottitis.[10, 11, 17]

Diagnosis is made on examination of the larynx by trans-nasal fibre-optic laryngoscopy, which may reveal an erythematous and congested epiglottis with inflammation of the surrounding supraglottic structures.[14, 18–21] Radiological investigations are usually unnecessary, although if an associated abscess is suspected then a CT scan may be useful.[22]

Treatment of epiglottitis

Patients should be admitted for observation in an appropriate setting such as an ENT department, high dependency or intensive care unit, depending on the status of the patient. It is important to manage these patients as a team, with involvement of anaesthetists and paediatricians appropriately. Despite advances in airway management, epiglottitis is still associated with mortality from associated complications and airway problems and early appropriate management is essential to minimize an adverse outcome.[23]

A tailored, selective approach based on careful evaluation of these patients is important and varies from conservative treatment with close observation to interventional treatment by an artificial airway for patients with respiratory distress or significant stridor. Close observation is mandatory as in a small number of patients progress from no respiratory distress to a significantly compromised airway may occur in just a few hours.[18] Advice on antibiotic treatment should be sought from microbiologists but in the first instance intravenous 3rd generation cephalosporins are recommended in conjunction with metronidazole if anaerobic bacteria are considered also to be causative.[11, 14, 15, 24]

Systemic corticosteroids and nebulized adrenaline may be used in patients with significant airway compromise. Most of the literature on use of these substances is based on a paediatric population presenting with croup. Although there is no clear evidence that it is an effective treatment,[12, 18] their use may be considered in patients with a compromised airway. A short course of steroids may help to decrease the airway inflammation, possibly decreasing the need for intubation.[16, 25] However, careful consideration should be given to this rather than using corticosteroids as a matter of routine, as the evidence on the role of corticosteroids is lacking.

Most patients will respond to medical treatment, showing an improvement within 24–48 hours, and this can be monitored by examination with trans-nasal fibre-optic laryngoscopy as well as monitoring clinical and biochemical parameters.[10] There is an association between patients reporting dyspnoea and the need for airway intervention.[10] Therefore, it is always important to consider the potential complication in epiglottitis of airway obstruction and if the airway is deemed to be at risk, then there should be a low threshold for intubation of the patient at a relatively early stage. This should be done in an operating theatre setting with an experienced anaesthetist due to the risk of occlusion of the airway with instrumentation of an inflamed larynx.[26] Tracheostomy should be required only rarely in very urgent cases where the patient has presented at a late stage and intubation is not possible; in a database study of epiglottitis in the United States, tracheostomy was performed in 3% of cases of adult epiglottitis.[17]

Epiglottic abscess formation is a recognized complication of epiglottitis, which has been reported to occur in 4–27% of cases; they occur mostly on the lingual surface of the epiglottis.[14, 18, 24, 27] Treatment usually requires surgical drainage and is associated with an increased risk of airway obstruction.[18, 28] Such cases must be managed in conjunction with an experienced anaesthetist due to potential complications of rupture of the abscess and airway obstruction.[29]

LARYNGOTRACHEOBRONCHITIS

Viral laryngotracheobronchitis (LTB) is the most common cause of stridor in children (also known as 'croup') and usually has a self-limiting course[30] in the majority of cases. However, in children progression to an impending airway can be more rapid when compared with adults due to the relatively narrow airway.[31] The symptoms of respiratory distress and biphasic stridor occur as a result of airway narrowing below the level of the glottis. It is not known why the subglottis is specifically affected in this condition.

Adult LTB is an uncommon condition that was first reported in 1990.[32] It is a community-acquired condition and tends to be more severe in adults than in children. Patients typically present with a sore throat, malaise, stridor and dyspnoea. Endoscopic examination will reveal subglottic oedema; the supraglottis is typically unaffected and appears normal.

Adult patients with LTB require admission and observation in an appropriate setting. Treatment with oxygen, steroids and nebulized adrenaline should be administered. Although it is thought that the majority of cases are as a result of a viral infection, broad spectrum intravenous antibiotics should be administered to treat any superadded bacterial infection.

If there is significant airway compromise not responding promptly to treatment then intubation by an experienced anaesthetist in an operating theatre setting should be considered.

PERTUSSIS

Whooping cough, or pertussis, is an acute illness caused by a gram-negative pleomorphic bacillus Bordetella, usually *Bordetella pertussis*. Endotoxins and exotoxins produced by the bacteria induce an inflammatory response, stop cilia functioning and cause epithelial cell necrosis. It is a notifiable communicable disease transmitted by coughing and sneezing that affects all age groups. Pertussis is most severe in children, particularly infants. Adults and adolescents may go undiagnosed and act as a reservoir of infection as they have a milder disease and a less severe cough.

Pertussis is the most prevalent vaccine-preventable disease. The WHO-expanded program of immunization has seen the number of children worldwide fully vaccinated rise from 5% in 1974 to 83% in 2008, avoiding 680 000 deaths per year. Still, 16 million cases were reported with 195 000 deaths, 95% in developing countries where immunization coverage is poor.[33] A paradoxical rise in the incidence of whooping cough in heavily vaccinated communities including the UK is as yet not fully understood.[34] Following 14 infant deaths in the UK in 2012, all pregnant mothers are now offered vaccination in the last trimester of pregnancy to maximize maternal

levels of immunoglobulin and facilitate passive protection of the newborn when most vulnerable in the first 3 months of life.[35]

Clinical features

Whooping cough presents with symptoms of a runny nose, dry cough and mild pyrexia, similar to a common cold. The cough occurs in prolonged paroxysms after one to two weeks and is followed by gasping and the characteristic whoop in children. Milder symptoms occur in adults and adolescences, classically presenting as a protracted cough rather than the characteristic 'whooping cough' of children.

Investigations

The diagnosis should be confirmed by serum serology and nasopharyngeal aspirate culture and assay, to determine causative organism, by polymerase chain reaction (PCR).

Management

Pertussis is usually not diagnosed until the cough has developed. A 7–14-day course of erythromycin is recommended, but this does not change the character of the cough or clinical course of the disease.[36] Erythromycin is thought to prevent patients from being infectious and is recommended as prophylaxis in affected households, but the effect has been described as modest compared with good quality vaccination.[37]

The cough should be treated symptomatically with cough suppressants; however, a systematic review of the use of steroids, β2-adrenergic agonists, pertussis-specific immunoglobulin, antihistamines or leukotriene receptor antagonists showed no clear evidence base for their use.[38] Alternative antibiotic choices options are clarithromycin, azithromycin and trimethoprin-sulfamethoxazole. Fluoroquinolones are also likely to be effective in adults but there are no supporting data of effectiveness.

BEST CLINICAL PRACTICE

- ✓ Pertussis should be considered in patients of any age presenting with a prolonged acute spasmodic cough of 3 or more weeks duration.
- ✓ Once recognized, treatment with a 7–14-day course of erythromycin should be commenced.

DIPHTHERIA

Diphtheria is caused by toxigenic strains of *Corynebacterium diphtheriae*, an anaerobic gram positive pleomorphic bacillus. Less commonly, when associated with consumption of raw dairy products, *C. ulcerans* species may be responsible. Toxigenic strains are lysogenic for one of a family of bacteriophages that carry the structural gene for the diphtheria toxin. Diphtheria, a preventable disease, was endemic in the UK until coordinated mass immunization was introduced in 1942. Classically transmission is by inhalation of droplets from the upper respiratory tract of an infected individual. It affects non-immunized children and susceptible adults, particularly the elderly. The usual site of infection is the tonsil and fauces, but it can also occur in the nasal cavities or spread to the larynx.

The last indigenous UK death from diphtheria was in 1982. The ease of world travel facilitates transmission and the vast majority of the 65 positive isolates recorded in England and Wales since 1986 were imported, predominantly from the Indian sub-continent, South East Asia and Africa. A 14-year-old boy who contracted diphtheria in Pakistan died in 1994.[39] High levels of herd immunity are essential to ensure and maintain disease control. Political instability amongst other factors lead to loss of blanket immunization and a diphtheria epidemic in Russia and the newly independent states of Eastern Europe. At its peak in 1995, more than 50 000 cases were recorded.[40]

Clinical features

Diphtheria causes a severe sore throat, malaise, pyrexia and nasal discharge if the nose is affected. Examination of the throat reveals a grey pseudomembrane, which may spread to affect the larynx. The cervical lymph nodes are enlarged and tender. An infected patient may become a carrier or clinically unwell depending on the host response, virulence and toxigenicity of the infective organism. If oropharyngeal diphtheria is suspected, a swab from the throat and or oropharynx should be obtained and screened for diphtheria. This should be considered in patients presenting with membranous or pseudomembranous pharyngitis/tonsillitis and/or following overseas travel or contact with a traveller to high-risk countries in the previous 10 days. Recent consumption of raw dairy products or recent contact with farm or domestic animals may suggest *C. Ulcerans* infection. Since *Corynebacterium diphtheriae* is not easily identified, throat swabs from all patients with sore throats should be separately screened. In the UK, positive isolates should be sent immediately to the reference laboratory for detection of the potent exotoxin 28.

Management

Treatment is with benzyl penicillin and antitoxin.[41] Acute airway obstruction should be managed accordingly, ideally with intubation. Close contacts and relatives should be immunized.

Complications

The diffusible exotoxin has a predilection for cardiac and renal tissue and causes myocarditis, arrhythmias and possible death. Neurological complications due to the exotoxin may develop a few weeks after the acute infection; the most frequent is soft palate paralysis but paralysis may also affect the diaphragm and the external ocular muscles. Other long-term sequelae include scarring of the

oropharynx and nasopharynx due to fibrosis and adhesion formation.

BEST CLINICAL PRACTICE

- ✓ A throat/nasopharyngeal swab should be obtained and screened for diphtheria in patients presenting with membranous or pseudomembranous pharyngitis/tonsillitis, particularly if there is a history of travel to a high-risk country in the previous 10 days, recent consumption of raw dairy products or contact with farm or domestic animals.[42]
- ✓ If diphtheria is suspected or diagnosed, benzyl penicillin and antitoxin should be administered.
- ✓ The airway should be monitored and, if obstructed, intubation should be considered.

INFECTIOUS MONONUCLEOSIS

Infectious mononucleosis (IM) or 'glandular fever' is a common disease caused by infection with the Epstein–Barr virus (EBV), a herpes virus. Sub-clinical infection is common although symptoms are often mild and self-limiting requiring minimal intervention. EBV has a special affinity for B lymphocytes, infecting the epithelium of the oropharynx and genital tract. It is transmitted via bodily secretions, most commonly saliva when kissing. Infectious mononucleosis is commonly seen in adolescents and young adults, with an incidence of up to 50 per 1000 persons.

Clinical features

Infectious mononucleosis has an incubation period of between 4 and 7 weeks.[43] Patients present with the classical features of sore throat, tonsil enlargement, cervical lymphadenopathy, periorbital oedema, especially of the lower lids (*Hoagland sign*) and fever. Palatal petechiae are more common in younger patients whereas hepatomegaly and jaundice are relatively more common in the older population. Splenomegaly is a late sign of infection and resolves within 3–4 weeks but fatigue and myalgia can persist for a number of months following resolution of the initial infection.

Investigation

Patients should have a full blood count (FBC), liver and renal function tests. Infectious mononucleosis is suspected if there is either a leucocytosis of >50% of the total white cell count (WCC) and 10% atypical leucocytes, or 20% atypical leucocytes.

The Monospot test and Paul-Bunnell test are types of heterophile antibody test. The Paul-Bunnell test is based on sheep red blood cell (RBC) agglutination, whereas the more sensitive and specific monospot test is based on latex agglutination using horse RBCs.[44]

Positivity to Monospot increases over the first 6 weeks of IM infection as the EBV heterophile antibody titres reach their peak; repeat testing 7 days later may be required. In the face of repeatedly negative Monospot tests, cytomegalovirus (CMV), human immunodeficiency virus (HIV), toxoplasmosis and rubella testing should be considered.

Management

As there is no specific treatment for infectious mononucleosis, supportive measures such as fluids, analgesia and rest are advised. Superimposed streptococcal throat infection may occur and antibiotic treatment required. Aminopenicillins such as amoxicillin or ampicillin should not be used due to the incidence of maculopapular rash. Acyclovir has not been proven to affect the outcome and is not advised in the management of uncomplicated infectious mononucleosis.[45] Corticosteroids improve pain scores and time to symptomatic resolution for pharyngeal infections, especially when given in combination with antibiotics.[46]

Complications

Airway obstruction due to cervical lymphadenopathy and tonsillar hypertrophy is a rare but potentially fatal complication of infectious mononucleosis.[47]

Other complications include anaemia, thrombocytopenia, encephalitis, transverse myelitis, Gullian–Barre syndrome, pericarditis and myocarditis.

Hepatomegaly resulting in jaundice and splenomegaly are late findings. Patients are counselled to avoid sport or vigorous activity due to potential splenic ruptures, the majority of which occur following minor trauma.[48] The rate of rupture is less than 1 in 500. Whilst recovery is usually quoted at 4–6 weeks, a small population of patients suffer prolonged fatigue, with 13% at 6 months and 4% at 2 years meeting the criteria of chronic fatigue syndrome.[49]

BEST CLINICAL PRACTICE

- ✓ Diagnosis of IM is by heterophile antibody test. The Monospot test is the most sensitive and specific test.
- ✓ Treatment is supportive.
- ✓ Steroids may aid in the management of the partially obstructed airway but intubation or tracheostomy are required when the airway is considered unsafe.
- ✓ Corticosteroid in combination with antibiotic treatment reduce pain scores and time to symptom resolution of pharyngeal symptoms.
- ✓ Amoxycillin should be avoided due to the risk of a macular rash in EBV infections.
- ✓ Patients should be counselled with regard to physical activity.

MYCOTIC LARYNGITIS

Fungal infections of the larynx are usually secondary to fungal inhalation in immunosuppressed patient with laryngeal mucosal disruption.[50]

Clinical features

Mycotic laryngeal infections are rare in patients with normal immune function; when they do occur they present as subacute or chronic infections. In contrast, immunocompromised patients, particularly those with haematological malignancy, are prone to acute infection from these opportunistic pathogens.[51] Mycotic laryngitis, with the exception of superficial candida infection, is usually associated with ulceration. Infections from candida and aspergillus are widespread but coccidioidomycosis, blastomycosis and histoplasmosis are endemic to specific geographical regions.

The larynx is probably affected by candida more often than realized and should be seriously considered in patients with refractory symptoms; up to 15% of patients with chronic laryngitis are diagnosed with mycotic lesions when examined.[52] In immune-competent patients, the most common predisposing factors are recent treatment with antibiotics, use of inhaled steroids,[53, 54] diabetes, chemotherapy, radiation therapy, smoking, acid reflux and inhalational or thermal trauma. Often, more than one predisposing factor is present. The characteristic finding in the larynx is a white pseudomembrane or adherent white plaque that can be mistaken for leukoplakia. It can also appear as diffuse erythema, with oedema and ulceration in severe infection. Whilst invasive candidal infections are rare, it is thought that colonization has an indirect effect on defence mechanisms and aids development of bacterial infections locally.[55]

Invasive aspergillosis is an opportunistic infection that occurs mainly in immunocompromised patients with haematological malignancies. Primary laryngeal aspergillosis is very rare, but recognition is important as steroids could have an adverse effect in affected patients with airway distress.

Investigation

Pulmonary fungal disease should be excluded and all patients with mycotic laryngitis should have a chest radiograph. Fungal trachea-bronchitis is generally limited to HIV-positive patients or the severely immunocompromised. Such cases present with stridor, fever and a productive cough.

Direct laryngoscopy and biopsy may be necessary to confirm a diagnosis of fungal laryngitis. It is of note that the more chronic fungal infections, such as blastomycosis, can present as a laryngeal mass requiring laryngeal biopsy for a definitive tissue diagnosis.[56] Special fungal stains, such as methenamine silver and periodic acid-Schiff, are required to identify the fungal hyphae. However, histology will not differentiate between the specific fungal species for which cultures are necessary.

Management

Systemic antifungal therapy is necessary for immunocompromised patients. Antifungal agents suppress fungal growth, making recurrent infection likely unless the underlying predisposing factors are addressed and corrected. Recurrence will also occur if the agent is used for too short a period or in an inadequate dose. Suitable agents include fluconazole, ketaconazole, itraconazole and amphotericin B. Each agent has its own characteristics: fluconazole for 3–4 weeks is the preferred agent for candida infection; itraconazole is particularly effective for aspergillus infections at a dose of 100–400 mg daily, monitored by regular blood levels; ketaconazole is the agent of choice for histoplasmosis and blastomycosis. Amphotericin B needs to be administered intravenously and also has significant adverse effects on the kidney, heart and liver.

BEST CLINICAL PRACTICE

- If acute mycotic laryngitis is suspected, immunodeficiency should be considered and investigated.
- Patients with a diagnosis of fungal laryngitis should have a chest radiograph.
- A direct laryngoscopy and biopsy is recommended in severe presentations and non-responders to initial therapy. Samples should be sent for histology and specific fungal cultures.
- A suitable course of a specific antifungal medication should be administered and predisposing factors should be addressed and corrected.

LARYNGOPYOCOELE

A laryngocoele is an abnormal dilation of the lateral most region of the laryngeal ventricle. The sac is lined with pseudostratified columnar ciliated epithelium, maintaining a connection to the ventricle. Laryngocoeles are described as internal, external or mixed. Internal laryngocoeles do not extend laterally through the thyro-hyoid membrane, external laryngocoeles exist lateral to the thyro-hyoid membrane, whereas mixed have both internal and external components. Laryngocoeles are more common in men and increase in incidence with age, though are still rare, with an incidence of 1 per 2.5 million per year.[56] The aetiology is unknown, with factors that increase intra-glottic pressure (e.g. glass blowing, trumpet playing, weight lifting) suggested as having a role in development. The laryngocoele normally contains air or mucus connecting with the airway. A laryngopyocoele forms when the neck of the sac become blocked and the laryngocoele becomes infected and contains mucopus.[57]

Clinical features

External laryngocoeles present commonly as a lump in the neck. It may possibly inflate on performing a Valsalva manoeuvre or may be emptied with external pressure (Bryce's sign).

Internal laryngocoeles may present with hoarseness, dysphagia or globus. Flexible nasendoscopy classically shows an enlarged and smooth swelling of the false cord, often making visualization of the cords challenging. Due to the association of laryngeal squamous cell carcinoma (SCC) within the ventricle and laryngocoele, it is advisable to carefully examine the area endoscopically.[58–60]

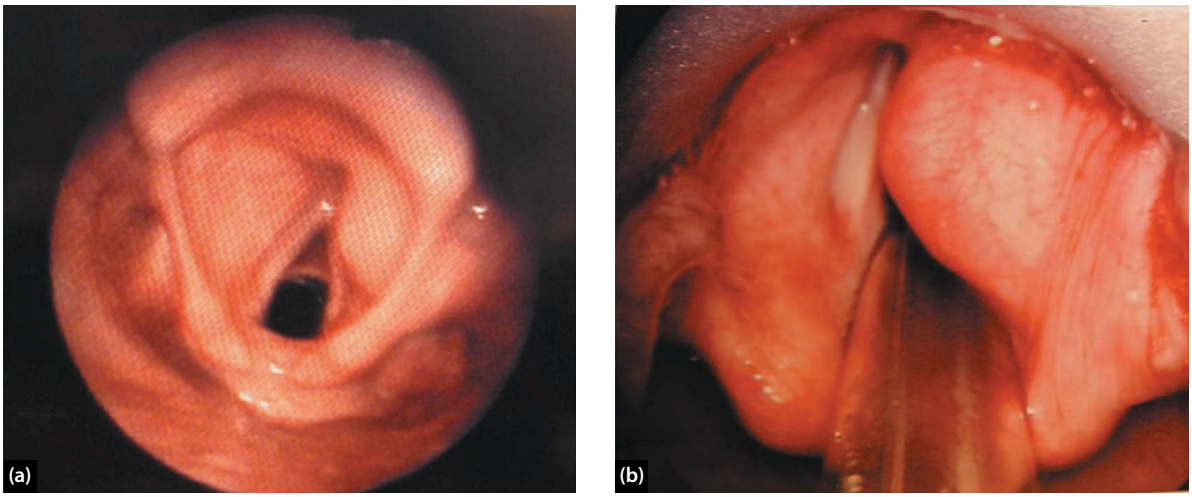

Figure 69.1 (a) Appearance of a right-sided laryngocoele as seen with a flexible laryngoscope. **(b)** Endoscopic appearance of right-sided laryngocoele at the time of surgery.

Laryngopyocoeles can present with pyrexia, dysphagia and potential airway compromise.[61]

Investigation

Cross-sectional imaging with CT allows delineation of cystic and laryngeal architecture. An MRI scan allows allows better characterization of soft tissue abnormalities.[62, 63]

Management

A patient with an evolving laryngopyocoeles may present as an acute airway emergency, stridulous and in respiratory distress. Definitive airway control via means of a tracheostomy or intubation may be required. For this reason surgical excision of laryngocoeles is advised prior to the evolution into a laryngopyocoele and the potential airway compromise. Patients presenting with a laryngopyocoele should be treated with intravenous antibiotics and dexamethasone, with needle aspiration of the external component if feasible. Following resolution of the infection a delayed excision of the laryngocoele is advised. Management can be either via the classical lateral external approach or endoscopically. Endoscopic excision using CO_2 laser has been shown to be effective in the management of the internal and external component.[64]

BEST CLINICAL PRACTICE

- Emergent airway management in cases of airway instability.
- Treatment with high-dose intravenous antibiotoics and dexamethasone.
- Tracheostomy placement if no improvement with conservative management.
- Early elective surgical excision.

KEY POINTS

- Consider early surgical management of laryngoceles to prevent a potential laryngopyocoele.
- Excision can be endoscopic or external approach.
- Laryngopyocoeles can cause airway obstruction

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CHAPTER 70

CHRONIC LARYNGITIS

Kenneth MacKenzie

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SEARCH STRATEGY

This search was carried out in conjunction with The Clinical Effectiveness Librarian, Glasgow Royal Infirmary, Greater Glasgow & Clyde NHS Trust and University of Glasgow using Medline, M base, and Pubmed to search with the following keywords: chronic laryngitis, aetiology, diagnosis and treatment.

INTRODUCTION

Chronic laryngitis is chronic inflammation of the laryngeal structures, most commonly affecting the laryngeal mucosa and to a certain extent the submucosa. The chronic inflammatory process can be due either to infectious or non-infectious causes, with a broad spectrum of aetiologies which may act singly or in combination. The chronic changes in the larynx can result in many laryngopharyngeal symptoms but the principal effect of the condition is a persistent and fluctuating change in voice and subsequent impact on the quality of life of the patient. The high prevalence of the main aetiological factors associated with chronic laryngitis, namely smoking and voice abuse, and the debated influence of reflux disease, whether it be laryngo-pharyngeal reflux or gastro-oesophageal reflux, results in the management of this condition being challenging in relation to both diagnosis and efficacy of treatment.

In 1976, Stell and McLoughlin commenced the debate around the aetiology of chronic laryngitis and concluded from their case controlled series that occupational effects had only minimal influence: smoking was no greater than in the control group, but that infection of the upper and lower respiratory tract was of significance.[1] Intuitively it would seem likely that the type of occupation, and associated environment might have a significant influence on the quality of the air, or the fumes inhaled, or how the voice might be used, for example, in the presence of background noise.

This has been supported by reports in various case series of the relationship between occupations and chronic laryngitis; with excess noise at work,[2] asbestos workers,[3, 4] cement workers,[5] solvents and shoe workers,[6] hairdressing,[7] and glass blowers.[8]

The association between the remainder of the respiratory tract and the larynx and possible concurrent aetiologies have been highlighted in reports relating to allergy.[9, 10] The underlying hypothesis is that allergens which cause adverse effects in the upper airways, such as the nose, nasopharynx and pharynx, are likely to have a similar effect on the larynx and hypopharynx. Whilst this may be the case, the more likely cause is through the use of inhaled drugs in lower respiratory tract disorders such as asthma and the overall management of

both nasal and paranasal sinus disorders. The effect of respiratory inhalers, not only with regard to their content but also their propellant, on the laryngeal structures is well documented and it remains a continuing challenge on how to balance the need for optimal treatment of the peripheral airways and improvement of the patients' ability to breathe, and subsequent quality of life, against the adverse effect of the inhaled drugs being present in the larynx and proximal trachea.

Significant debate exists about the aetiology and subsequent management of chronic laryngitis in the setting of gastro-oesophageal reflux (GORD) and laryngopharyngeal reflux (LPR). It would appear from the literature that clinicians consider a relationship to exist between these disorders,[11] but how this is diagnosed and ultimately managed effectively remains a significant challenge to all of those dealing with disorders in each of these subsites. A detailed treatment of GORD and LPR can be found in Chapter 77, Reflux disease.

Chronic laryngitis can be caused by a wide variety of infective organisms. Perhaps the most graphic example is seen with candidal infection affecting all areas of the upper aero-digestive tract, seen in patients with underlying immunocompromise, diabetes mellitus, after chemoradiotherapy or following prolonged antibiotic administration.

This spectrum of disease in the larynx will be considered in two main sections: the clinical diagnosis of general diffuse laryngitis with no identifiable cause and specific forms of chronic laryngitis due to rare but recognized aetiologies.

CLINICAL PRESENTATION

History

The key symptom associated with chronic laryngitis is alteration in voice quality in the form of hoarseness (dysphonia). In trying to differentiate this from other forms of dysphonia, the voice in chronic laryngitis generally tends to be rough or coarse, and may have an overall reduction in the pitch. It tends to develop gradually with an insidious onset and may be present for several months or years. The hoarseness is persistent with the voice being seldom, if ever, normal but it is rare for there to be aphonia.

There may be associated symptoms with the chronic laryngitis such as difficulty in swallowing (dysphagia), a sensation of something being in the pharynx, painful or strained speaking , throat ache or discomfort, throat clearing, persistent non-productive cough, halitosis, unusual taste or bitter taste, otalgia, water brash or indigestion.

It is important to establish the concerns of the patient with regard to any underlying issues such as their worry of the risk of malignancy through to whether they want complete resolution of their voice and upper aero-digestive problems. It may be that the patient has been a long-standing smoker and simply wants to be reassured that there is no malignancy or alternatively that they are a professional voice user, such as a teacher, whose voice problems are a result of the chronic laryngitis, preventing them from fulfilling their professional obligations. It is essential to establish the effect a patient's dysphonia on various spheres of activity, as it is well recognized this dysphonia has an overall impact on their quality of life.[12–15] To a certain extent this will influence, and possibly determine, the aims of the subsequent assessment and treatment strategy.

Having established the principal characteristics of the dysphonia, and associated symptoms, there are other key elements of the history which are important to elucidate with regard to potential aetiological factors. Clearly, these aetiological factors can act singly or in combination:

- Smoking: A key factor in chronic laryngitis. The type, frequency and duration of smoking should be noted.
- Reflux: Laryngopharyngeal symptom matrix may indicate possible reflux type. Past history of upper GI dysfunction such as *H Pylori* infection, upper GI investigations including gastroscopy, pH monitoring or manometry and possible upper GI surgery should all be noted.
- Patient's occupation: The working environment should be identified as it might highlight the environmental quality of air or presence of fumes and the noise level in which the patient has to communicate.
- Social activities: The type and environment of social activities should be noted as this may aggravate chronic laryngitis.
- Allergies: Both proximal and distal aero-digestive tract and their treatment.
- Co-existent disease which may be associated with chronic laryngitis such previous radiation therapy for head and neck malignancy, immuno-suppressed states, diabetes, and diseases associated with specific types of chronic laryngitis such as tuberculosis, sarcoid or granulomatosis with polyangiitis (previously called Wegener's granulomatosis).

Irrespective of the causation, the unrelenting effect on the voice, the co-existent laryngopharyngeal symptoms and the subsequent impairment on the ability of an individual to communicate and carry out their daily functions, either on a professional basis or socially, has a significant impact on their quality of life. Given both the chronicity and the relationship to long-established habits, there is a considerable challenge to try to improve the symptoms associated with this condition.

ASSESSMENT

Outpatient setting

Assessment of a patient with dysphonia starts during the consultation. During this time both consciously and subconsciously the clinician is assessing the quality of the patient's voice in relation to their history. Specifically, with regard to chronic laryngitis the severity of the dysphonia harshness and breathy components, strained intonation of the voice, associated tension and anxiety are all assessed.

Comprehensive assessment of the ear nose and throat is necessary. Examination of the ears and hearing should be carried out as it is important to establish that the hearing is within normal limits and rehabilitated appropriately. With regard to the nose it is necessary to establish if there are any significant nasal abnormalities which might result in persistent obstruction or mouth breathing, and whether or not there is any evidence of allergic rhinitis. Per-oral pharyngeal examination is carried out to ensure there is no significant oral or oropharyngeal pathology which might be associated with smoking, as well as identifying significant caries or candidiasis.

The key investigation in the management of this type of patient is examination of the larynx in the resting and neutral state. This is best achieved by fibreoptic nasendoscopy examination. To facilitate this, the nose can be prepared with topical decongestant and local anaesthetic agent such as Cophenylcaine. This anaesthetizes and vasoconstricts the nasal mucosa so allowing easier passage of the nasendoscope. The disadvantage of such a preparation is that patients frequently find it unpleasant, both in the application of the nasal spray due to its effervescent component and also the taste associated with it.

If a more detailed examination of the structures of the larynx is needed then per-oral rigid laryngoscopy is carried out, having applied some form of topical anaesthesia to the oropharynx. This is generally coupled to a camera system and may be used with or without stroboscopy. This combination of examination techniques allows more detailed examination of the structure and movement of the vocal cords and possible asymmetry as this may indicate any potential underlying malignancy or other pathology such as cystic lesions of the vocal cord.

The principal aim of these outpatient assessments is to determine whether microlaryngoscopy under general anaesthesia is required. This is generally determined on the level of suspicion following the outpatient examination with regard to the presence or otherwise of localized or discrete abnormal areas in shape and/or colour. If there is any concern about the presence of malignancy, this should precipitate the need for microlaryngoscopy.

Frequently, however, there are only vague, non-specific diffuse oedematous alterations in colour and structure, the combination of which may result in a provisional clinical diagnosis of chronic and inflammatory laryngitis.

The abnormalities may affect all subsections of the larynx, e.g. all of the true cords or be restricted to specific areas. Clinical experience suggests that there is considerable inter- and intra-observer variability when assessing the larynx in the outpatient setting. Pontes et al. reported in a case series of 85 patients with multiple benign laryngeal pathology that there was frequent inter-observer variation in relation to diagnosis of each of the pathologies involved.[16]

Given the wide range of non-specific appearances within the larynx, several workers have suggested descriptive criteria on which to base the recording of the assessment of the chronic laryngitis. This is a necessity when trying to evaluate treatment strategies, the most notable of which is the treatment of gastro-oesophageal and laryngo-pharyngeal reflux. An example of this is by Feehs and Koufman[17] who described the spectrum of findings without a numerical grading system. The grading system was hierarchical as follows:-

1. Red arytenoids and piled up into the arytenoid mucosa.
2. Diffuse oedema, including Reinke's space, mucosal thickening but possibly minimal erythema.
3. Diffuse oedema with granular friable mucosa.
4. Discreet granulomas, with or without, oedema and erythema.

Intuitively, it would seem reasonable to conclude that reasonable inter- and intra-observer repeatability can be achieved if there is a discrete lesion such as a granuloma and more specific pathology such as Reinke's oedema. However, with regard to chronic laryngitis, it is unrealistic to expect any repeatability that would be clinically meaningful.

In an attempt to try to achieve this, photographic recording of either the flexible or rigid endoscopic findings is advocated. Despite doing this, there is a still subjective assessment of these images which is open to a similar difference and variation in interpretation as in a 'live' examination.

At this stage, operative assessment may not be deemed appropriate in that the treatment may be principally non-surgical or medical, such as in chronic non-specific laryngitis, or because the patient does not wish any alteration to their voice, such as in Reinke's oedema or in vocal cord nodules. It may therefore be more appropriate to refer patients to speech and language therapy for consideration of a course of voice therapy.

OPERATIVE ASSESSMENT

The need for endoscopic assessment under general anaesthesia is established in the outpatient setting. A significant proportion of patients with apparent inflammatory changes within the larynx will require further assessment by carrying out microlaryngoscopy under general anaesthesia for the following principal indications:

- Any area of the larynx which might be considered suspicious with regard to dysplastic changes or overt malignancy.
- Co-existent pathologies such as vocal cord polyp, which need surgical management.
- Inability to examine the larynx comprehensively due to the patient not being able to comply due the larynx being obscured, for example by the presence of crusting of secretions.
- Failure to respond to medical treatment.

To facilitate the best operative view when carrying out the procedure, it is necessary to have appropriate maintenance of ventilation. A technique that allows completely unobstructed view while allowing visualization, whilst at

the same time facilitating the use of the CO_2 laser, is that of supraglottic jet ventilation. The disadvantage of this is that the effectiveness of this ventilation using capnography cannot be assessed readily, which may be relevant in patients with chronic obstructive airways disease. A more stable and secure way of ventilating the patient is to use a microlaryngeal tube, size 5 or 5.5, which has the added advantage of protecting the airway in the event of gastro-oesophageal or laryngo-pharyngeal reflux. The disadvantage is that it partially obscures the view of the vocal cord and has to be converted to a specific laser endotracheal tube of a similar size should the CO_2 laser be used.

The compromise is to ventilate using a subglottic form of jet ventilation such as the Hunsacker Mon-jet ventilation system. This small tube sits in the posterior commissure and allows a greater view of the larynx but at the same time ventilates in a more controlled fashion than the supraglottic jet ventilation. It has the added theoretical advantage that the end tidal CO_2 levels can be determined.

The patient's larynx is assessed using 0, 30 and 70 degree rod lens endoscopes so that the type and extent of any lesion or lesions can be determined. If the lesion is discrete then excision biopsy, if at all possible, should be carried out. This is generally done using cold instrumentation to resect the lesion carefully from the underlying structures with minimal trauma, resulting in a histopathological diagnosis with no change, or only minimal change, in the voice.

If there are diffuse changes throughout the larynx a representative biopsy should be taken and this can be carried out using a cupped biopsy forceps such as a 4 mm type. However, this is a significant size and it may be more appropriate to take the biopsy using cold instrumentation and excise a specimen assuming an appropriate amount of submucosal tissue is incorporated into the specimen. Consideration should be given to the position and amount of tissue to be removed. If there is a diffuse, but uniform appearance, then a representative specimen should be taken from an area unlikely to affect the voice. Such an area would be the superior, super lateral aspect of the vocal cord or from the supraglottis.

HISTOLOGICAL FEATURES OF CHRONIC LARYNGITIS

Microscopy reveals benign mucosa usually covered by squamous epithelium of variable thickness with a tendency to keratinization. The active changes are present in the epithelium but no convincing epithelial dysplasia is identified. The lamina propria may be oedematous and contains a chronic inflammatory infiltrate of variable intensity including lymphocytes and macrophages. A light scattering of acute inflammatory cells is also often present. Patchy permeation of the surface epithelium by the inflammatory cells commonly occurs. There is variable degree of fibrosis of the lamina propria and prominent small vascular channels may be seen.

There is a need for robust classification which reflects the histological characteristics of chronic laryngitis. The principle is that in a certain proportion of patients who have chronic laryngitis there may be characteristics of their disease state which are liable to undergo potential malignant change. There is therefore a need to identify the cohort of patients in whom treatment may have to be more aggressive with closer monitoring. The most widely used system is the WHO grading for dysplasia into mild, moderate and severe. However, this system is prone to low interrater agreement. An alternative is the Ljubljana classification system that has been in use for several years. Gale et al. reported in a retrospective case series the Ljubljana classification of laryngeal lesions in relationship to subsequent malignant transformation. The hyperplastic laryngeal lesions (n = 4574) were graded into simple, abnormal, atypical hyperplasia (risky epithelium) and carcinoma *in situ*. Malignant transformation in the atypical hyperplasia was 11.6% whereas in the benign group, simple and abnormal, it was 0.3%. From this analysis, the authors concluded that this classification system was of value with regard to identifying potential malignant transformation.[19] This has recently undergone further clinical validation and a change in nomenclature (current terminology is low-grade squamous intraepithelial neoplasia (SIL), high grade SIL, carcinoma-*in-situ*), with a detailed description of the morphologic criteria for these groups. The management of dysplasia is discussed elsewhere in the book, with consensus recommendations on treatment and follow up.

NON-SPECIFIC LARYNGITIS

Non-specific laryngitis is a common condition presenting with persistent and unrelenting dysphonia which can vary in quality, severity and duration. Depending on the aetiology, it may result in only a mild effect on the quality of the voice or render the patient's voice harsh leading up to aphonia. Associated with this change in voice, patients may have symptoms such as pain or discomfort in their throat, description of an awareness in their throat with globus pharyngeus type symptoms, halitosis or otalgia, or the report of symptoms of excess catarrh with persistent throat clearing. The most frequently implicated aetiological factors are smoking, voice abuse, and reflux disease, namely gastro-oesophageal reflux and laryngo-pharyngeal reflux.

To further challenge the clinician's comprehensive management of this disease is the wide range of clinical features which may be associated with the clinical diagnosis of non-specific laryngitis. These features can range from localized specific appearances within the larynx through to complete and diffuse changes in the larynx rendering the larynx almost unrecognizable from its normal appearance. Furthermore, this multiplicity of aspects of the disease process renders the assessment of the disease, and efficacy of any of the treatment strategies, extremely difficult. It may therefore be that the management of this ill-defined wide-ranging condition may have to be pragmatic by targeting management, by identifying potential

aetiological factors, confirming the diagnosis, initiating treatment and finally investigating or further modifying treatment should this pragmatic approach not improve the patient's symptoms.

IDENTIFYING THE POTENTIAL AETIOLOGY

Given the key aetiological factors, it is likely that they will vary in influence from country to country and within countries. Despite this epidemiological variation, it is likely that the most common aetiological factor in non-specific laryngitis is that of smoking which in turn may be the most challenging aspect of the disease to manage.

Intuitively, it could be expected that chronic contamination, or infection of the larynx, might be the key in generating a chronic laryngitic picture. Some authors have found that septic foci are present,[20] whilst others have not been able to demonstrate bacteria in chronic inflammatory laryngeal samples,[21] while other groups have demonstrated the presence of bacterial biofilm.[22] Furthermore, in relation to specific bacteria, *H pylori* has been identified in those patients with chronic laryngitis and laryngeal cancer[23, 24] and so the question arises to whether eradication strategies should be implemented in this group.[25] The specific role of bacteria continues to be debated and it would seem a rational approach to treat any overt bacterial infection, whether it involves the larynx directly or indirectly as a secondary effect caused by lower respiratory tract infection with the subsequent indirect traumatic effect on the larynx caused by coughing and expectoration.

A common potential aetiological factor is voice misuse or abuse. If an individual has to use their voice for a significant period of time in an environment which might be irritating, or where they may have to raise the volume of their voice over a significant period, then it is likely that they may develop secondary inflammatory changes in the larynx in response to the voice usage. If, following this period, there is not sufficient time for compensatory rest then the acute laryngeal changes may become chronic, particularly if the process of voice misuse is repeated on a regular basis.

The third key potential aetiological factor implicated in chronic non-specific laryngitis is reflux disease. When considering this potential aetiological factor, there is reliance on the other symptoms which may be present due to reflux, both gastro-oesophageal and laryngopharyngeal. Although there are other types of reflux, these are the two which are primarily implicated in most discussions around the evidence relating to chronic laryngitis and reflux. The recognized symptoms associated with reflux disease and chronic laryngitis are those of globus type symptoms of awareness in the throat, persistent throat clearing, alteration in the voice, altered taste in the mouth, and possibly symptoms of heartburn or indigestion.

The relationship between potential reflux and the symptoms associated with chronic laryngitis are based on two main hypotheses, firstly that of the direct contact and contamination of the upper airways by gastric acid or refluxate, in some cases pepsin, and secondly by the vaso vagal reflex triggered by acidification of the distal oesophagus. The association between ENT symptoms, not just those of chronic laryngitis, and reflux are well recognized and published widely.[26]

DIAGNOSIS

The majority of patients diagnosed with non-specific laryngitis are based on examination in the outpatient setting by identifying a group of signs present in the larynx on examination using the fibreoptic nasendoscope or the video-stroboscope having established an appropriate history. The key features of non-specific laryngitis are a diffuse inflammatory picture with widespread irregular mucosa, varying degrees of oedema, erythema, exudate, but inevitably with distortion of the normal anatomical features in a diffusely irregular and swollen manner. Given that a high proportion of these patients will have smoking as an aetiological factor, a key clinical decision is whether or not there may be any cancerous or precancerous elements in the larynx. If it is not possible to state unequivocally that the laryngeal appearances, although diffuse, are in keeping with a completely benign picture then the larynx will need to be examined in more detail by microlaryngoscopy, and representative histology of the laryngeal surfaces obtained. In severe cases, there may be gross abnormalities of the larynx with the surface mucosa being obscured by the presence of a substantial amount of exudate this covering possibly being dried and crusted, so obscuring the clinical picture. It is frequently necessary in this group of patients to irrigate the larynx with saline during microlaryngoscopy to ensure that detailed assessment and subsequent appropriate biopsy can be carried out without initially traumatizing the inflamed larynx by direct instrumentation by laryngeal suction.

In many patients, the diagnosis will be made on the symptom complex and the clinical examination. To try to aid in the differentiation between the various aetiological factors, methods of assessing potential contribution of reflux have been suggested. The most frequently one advocated is the Reflux Symptom Index (RSI) the validity and reliability of which were initially described by Belafasky et al, who described evaluation of this self-administered nine-item outcome instrument for LPR in relation to the Voice Handicap Index (VHI).[27] Although this relates specifically to the assessment of the RSI as a patient report tool in comparison to VHI, it did demonstrate that patient reported voice disorders had a significant improvement following empirical PPI treatment in those suffering from chronic laryngitis. The use of the RSI in conjunction with other patient reported voice outcome measures, namely the VoiSS, has been reported by Beech et al. again with good correlation.[28] In this group, acid suppression therapy was shown to be of some benefit in chronic laryngitis patients without troublesome reflux symptoms the RSI and the VoiSS scores both being improved with Proton Pump Inhibitor prescription and voice therapy carried out by Speech and Language Therapy.

To aid in the diagnosis of the possible influence of reflux in the larynx it has been suggested that the Reflux Finding Score (RFS) may be used and previous reports have shown

that although this is a sensitive method picking up pH proven reflux patients specificity may be quite low, with a sensitivity of 87.8% specificity of 37.5% respectively.[29]

The principal aim of having any of these scoring systems is to try to establish a process which would have a low inter- and intra-observer variability with a high level of repeatability so that treatment strategies can be evaluated comprehensively.

TREATMENT

If each of the investigations carried out identify that the laryngitis is indeed non-specific then the treatment that is used will address each of the main aetiological factors of smoking, voice use, and reflux.

Robust, evidence based smoking cessation strategies are currently available, ranging from counselling and behavioural therapy through to pharmaco-therapy including nicotine replacement, Varenicline and Bupropion sustained release.[30] Although this commitment and drive is present in cancer groups, in realistic terms it may be more difficult to persuade someone with chronic laryngitis to stop as at this stage there would be no life threatening condition present.

Voice misuse or abuse, must be addressed and is the main stay of treatment of chronic laryngitis is addressed in detail in Chapter 66, Speech /voice therapy for voice disorders.

The therapy designed by the speech and language therapists is comprehensive not only in relation to the laryngeal structure and function but also addresses aspects of lifestyle and voice use by discussing vocal hygiene and addressing dysfunctional components of voice production. This subtle combination of history taking, diagnosis, treatment planning and execution and 'ad hoc' psychotherapy has been recognized in the past to be of clinical value. There had, however, been little evidence in support of its use except for some level 3 evidence from short case series for voice therapy being used in specific conditions such as vocal cord nodules or Reinke's oedema.[31] In 2001, MacKenzie et al. reported a randomized controlled trial of the use of voice therapy in a heterogenous group of voice patients who had conditions which one would normally expect to see benefit from voice therapy namely vocal cord nodules, functional dysphonia and chronic laryngitis. The principal outcome from the study, patient self-report, was significantly better in the group who received voice therapy when compared with the control group of observation only.[14] The voice therapy used was based on the reported consensus of treatment by UK Speech and Language Therapists in a group of laryngological disorders, one of them being chronic laryngitis.[32] The study results indicate that referral to the Speech and language therapy team for voice therapy is highly appropriate and of benefit to those suffering with chronic laryngitis.

The most contentious area in the treatment of chronic laryngitis is that of precipitating or concurrent reflux disease. There is a wide range of evidence trying to address the issues surrounding the treatment of reflux disease. The extra oesophageal manifestations of those patients suffering from laryngo-pharyngeal reflux or gastro-oesophageal reflux disease are covered in detail in Chapter 77, Reflux disease. Delahunty described inflammation of the posterior third of the vocal cords associated with GORD on barium swallow and subsequent successful symptomatic treatment with antacid. This possible association between GORD and chronic laryngitis was initially known as acid laryngitis.[33]

In an observational series in 1982, Ward et al. described a group of 86 patients with chronic non-specific laryngitis which they hypothesized was due to local irritation by chronic coughing and throat clearing which in turn was secondary to a hiatus hernia and gastro-oesophageal reflux.[34] This hypothesis was tested further, and much more 'invasively', in a surgical series by Deveney et al. In a cohort of 13 patients with chronic non-specific laryngitis and confirmed GORD the performance of a Nissen fundoplication resolved the laryngeal problems in 11 (73%). This small study group was very carefully selected in that each patient had ceased smoking for at least six months. The conclusion was that surgical correction of the GORD in a select group of patients will resolve the laryngeal problems.'[35] However, it could clearly have been the cessation of the smoking which had the greater influence.

There are two principal theories to explain the pathophysiology. Firstly, the refluxate from the stomach and oesophagus crossing the upper oesophageal sphincter can cause an inflammatory effect on the laryngo-pharynx. Secondly, chronic repetitive throat clearing and coughing which is caused by a vagally mediated response from the oesophagus can indirectly cause laryngitis.[36] If either, or both of these theories, is correct then there should be an increased prevalence of laryngeal disorders in patients suffering from oesophagitis.

El-Serag and Sonnenberg demonstrated in a large case controlled series of patients with erosive oesophagitis (n = 101, 366) the higher statistically significant odds of laryngitis (odds ratio shows 2.1; 95% CI 1.53 to 2.63). This would strongly support this hypothesis.[37]

This study supports the empirical treatment of extra oesophageal manifestations of reflux disease, of which chronic laryngitis is only one. This empirical practice has been widespread in patients with laryngopharyngeal symptoms, with or without, gastro-oesophageal reflux symptoms. A frequently quoted study was carried out by El Serag et al. in 2001 to test the validity of this treatment strategy. A randomized controlled trial of PPI versus placebo was performed in a group of patients (n = 22) with chronic laryngitis. Following confirmation of the disease status by upper GI endoscopy 24 hour oesophageal, and pH monitoring, laryngoscopy, and symptom questionnaires, the patients were randomized to receive either Lansoprazole 30 mg bd or matching placebo for three months. The primary outcome of complete resolution of laryngeal symptoms was seen in 6 of the Lansoprazole group compared with 1 (10%) of the placebo group ($p < 0.05$).[38] The authors concluded that empirical treatment with Lansoprazole is efficacious when relieving symptoms of laryngitis compared to placebo but with a cautionary note that the study was carried out in patients with a high chance of having

GORD and that it would have to be repeated in the general population if it was to be universally applied to all patients presenting with laryngeal symptoms.

Essentially, the treatment strategies can be split into those who believe that it is appropriate, and indeed advisable, to treat potential reflux disease empirically[39–46] and those who do not.[47–49] The indications and thresholds for this treatment can vary enormously with the indications being fairly minimal and the treatments used being wide ranging. The commonest treatment advocated is the prescription of a PPI where the main protagonists would suggest a strategy where it should be tried for several weeks and if does not succeed then perhaps change in this treatment with change of PPI dosage or supplementation or augmentation by other treatment such as antacids and alginates.[50] Those who do not support this strategy would suggest that widespread non-specific or non-targeted treatment of such populations result in inappropriate treatment with the sequelae in individuals such as rebound and excess gastric secretion and altering the bacterial flora profile of a population.

Whilst it might be considered medically appropriate to carry out tests to determine the presence or otherwise of reflux, and indeed the type of reflux, a pragmatic approach to this very common disease management is frequently indicated. On balance, there is a majority of clinicians who have the view that at least a trial of anti-reflux medication in the form of a PPI, with or without an alginate, and in these patients in whom there is not an appropriate response when one is expected or anticipated then it would be necessary to proceed to more detailed and more specific investigations. This is supported by a meta-analysis by Quadeer et al, who concluded that 'PPI therapy may offer a modest, but non-significant, clinical benefit over placebo in suspected GERD related chronic laryngitis' and recommended that validated diagnostic guidelines be used to facilitate the recognition of the patients most likely to respond to PPI treatment.'[51]

This relatively unsatisfactory state of affairs regarding treatment does appear to be the current practice. We advocate that that clinicians carry out treatment strategies on assessment of patients on an individual basis rather than having a blanket strategy of simply giving each patient anti-reflux medication.

CHRONIC LARYNGITIS AND MALIGNANCY

The relationship between gastro-oesophageal reflux and laryngopharyngeal reflux disease in chronic laryngitis, laryngeal dysplasia, has been widely debated for many years.[52, 53] The difficulty, however, is trying to identify studies without the confounding effects of other possible aetiological factors such as tobacco and alcohol. From a practical perspective, however, a high number of patients with chronic laryngitis will be smokers and as such will be exposed to the carcinogenic effects of smoking. It is clear therefore that a proportion of these patients who will have been diagnosed initially as having chronic laryngitis will progress to invasive squamous cell carcinoma. It is likely, however, that this diagnosis may have co-existed with early dysplastic changes with the latter subsequently transforming into frankly invasive malignancy. This therefore would be co-existent pathologies rather than malignant transformation from chronic laryngitis itself. Irrespective of the origins the level of clinical suspicion and treatment need to be the same.

KEY POINTS

- Aetiologies generally multi factorial.
- Main aetiological factors are smoking, voice abuse, LPR and GORD, and environmental factors.
- Empirical treatment with PPI can be considered.
- Supplementation with alginates can be considered.
- Voice therapy is advised.
- Stopping smoking and lifestyle modifications would appear appropriate.

REINKE'S OEDEMA

This is a distinct form of chronic inflammation of the larynx and so theoretically falls into the category of chronic laryngitis. Pathologically, there is a chronic state of oedema in the membranous portion of both vocal cords from the anterior commissure to the vocal process, hence other terms used are polypoidal degeneration or hypertrophy.

The disease has a predilection for females in middle age, with co-aetiological factors of smoking and voice abuse, and invariably presents with dysphonia with an overall reduction in pitch of the voice and rarely with obstructive symptoms. Laryngoscopic examination shows that the vocal cords appear uniformly, diffusely swollen with a bulbous appearance with normal mobility.

Combined modality treatment is needed to optimize the resolution of the condition. The pathological changes within the vocal cords need surgical treatment. The inflammatory process results in an accumulation of fluid within Reinke's space, the potential space between the vocal ligament and the overlying mucosa. The aim of surgical treatment of this condition is to remove the fluid and reduce the excess mucosa with minimal damage to the underlying laryngeal architecture. This technique was described initially by Hirano.[54] An incision is made in the laryngeal mucosa overlying the superior aspect of the true vocal cord in its long axis. Reinke's space is entered, the submucosal fluid contents aspirated and the excess mucosa trimmed. The technique can be carried out either by using cold techniques or the CO_2 laser. The theoretical disadvantage of the CO_2 laser is the injurious thermal effect on the surrounding tissues. Although this may be the case in other laryngeal disorders, it could be argued that the fluid in Reinke's space is sufficient to absorb the heat. A further potential disadvantage is that the specimen may be either severely carbonized or non-existent. Dissection of the excessive mucosa can be relatively easily carried out with minimal trauma. Although both techniques have been practiced widely there is little evidence in support of one rather than the other. In a case series of 36 patients

Lumpkin et al. compared 'stripping', CO_2 laser and the Hirano technique and concluded that the Hirano technique was preferable.[55] Although there have been advocates of the use of microdebriders in this situation there is little substantive comparative evidence in its favour. Overall, to satisfy the original aim of the surgery the use of microlaryngeal cold instrumentation is advocated.

If the patient is a smoker, as is frequently the case, smoking cessation strategies should be adopted. Hojslet et al. described a case series of 29 patients in whom a stopping smoking strategy was supported strongly. This consisted of nicotine chewing gum being freely available and group counselling supervised by a psychologist. Eight of them (28%) refrained from smoking and although the discomfort was reduced none of the voices returned to normal. While the diffuse laryngitic appearances resolved, the laryngeal oedema persisted.[56]

To rehabilitate the consequences of voice abuse and poor vocal hygiene a course of voice therapy should be undertaken.

If left untreated, the concern is that there may be malignant transformation. There has been little reporting of such a phenomenon, and from clinical experience it would seem more likely that the converse is the case, i.e. that the presence of bilateral symmetrical Reinke's oedema would suggest that it is very unlikely that there is malignancy present. The exception to this observation would be in the case of unilateral 'Reinke's' oedema where clearly such a finding could be oedema associated with a deeply centred malignancy such as a squamous cell carcinoma in the laryngeal ventricle.

KEY POINT

- Treatment should be cold surgery of the laryngeal lesion, smoking cessation and voice therapy.

VOCAL CORD POLYPS

Inflammatory changes restricted to a small area of the vocal cords, for example, after some form of vocal trauma such as shouting, can transform into vocal cord polyps.

Occurring more often in young to middle aged male smokers, these patients present with a history of persistent dysphonia. Nasolaryngoscopy will show discrete lesions arising from the true vocal cords, usually in the anterior two thirds. Surgical excision of the polyp(s) by microlaryngoscopy under general anaesthesia using cold instrumentation techniques is usually curative. There is a plane of cleavage at the base of the polyp between the polyp and the vocal ligament. Following topical application of adrenaline (1 in 1000) to the vocal cord polyp, the polyp can be held in micro-forceps, retracted medially and dissected from the mucosa overlying the vocal ligament with preservation of its integrity. This latter aspect is imperative if the normal function of the vocal cord is to be restored. Once the lesion has been excised a period of voice rest for at least 48 hours is generally advocated. The evidence in support of both the type and duration of altered/reduced voice use is low level and scanty. Intuitively, however, it would seem highly appropriate to arrange a course of voice therapy to correct any habits of voice misuse in the patient as it was voice misuse which was the cause of the polyp initially.

KEY POINT

- Vocal cord polyps treated by surgical excision and voice therapy

AMYLOIDOSIS

Amyloidosis can affect the larynx as part of a primary or secondary process of systemic amyloidosis. The deposits of amyloid, proteinaceous aggregates, have a high fluid content and can occur as a diffuse submucosal process or as small subepithelial masses. The patients present with dysphonia because of the presence of the deposits in the various subsites of the larynx and their effect on the vocal cord mobility. Ultimately there may also be an effect on the airway. The mainstay of treatment is microlaryngeal surgery to remove the deposits with minimizing the laryngeal damage and this can be by either cold techniques or by CO_2 laser. The use of CO_2 laser tends to be effective because of its ability to vaporize the high fluid content within the deposits. Diagnosis is confirmed histologically because of the affinity of the amyloid for Congo Red.

TUBERCULOSIS

Invariably, tuberculosis (TB) occurs with the pulmonary version of the disease, with the patient complaining of dysphonia, pain on speaking and swallowing, and otalgia. There is a diffusely reddened and oedematous larynx affecting predominantly the posterior one third of the glottis. There may be ulceration and the appearances can be confused with squamous cell carcinoma. Thus, it is imperative to obtain histological confirmation before embarking on radical treatment. Diagnosis is made by biopsy of the laryngeal tissues. Histological examination demonstrates granulomas with caseating necrotic centres, Langhans-type giant cells and mycobacterium organisms. Treatment is to secure an airway followed by antituberculous drugs. If timely there should be resolution of the laryngeal and pulmonary disease and if not there will be the effects of chronic inflammation with stenosis and vocal cord fixation.[57, 58]

SYPHILIS

The larynx is rarely involved in this rare condition. Although each of the stages may occur the secondary and tertiary stages of the disease are more common. Hoarseness and dysphagia are common but pain is rare. There are diffuse erythematous papules (secondary stage) and nodular infiltrates coalescing into painless ulcers (tertiary stage), with the epiglottis and ary-epiglottic folds being principally involved. Appearances are similar to those of TB and carcinoma, with the diagnosis achieved by positive syphilis serology. Treatment is with high dose penicillin.

LEPROSY

Like TB laryngeal involvement in leprosy (also known as Hansen's disease) occurs only when there is concurrent systemic disease. Invariably there will be cutaneous lesions which may have been present for several years with the nasal cavity frequently being affected. In the larynx the supraglottic is often involved, in particular the epiglottis, showing an oedematous, nodular supraglottis with ulceration. The dysphonia is of a muffled voice quality. The diagnosis is achieved by biopsy of this area with isolation of *Mycobacterium leprae* from the tissues. Treatment is with diaminodiphenylsulfone, rifampicin and clofazimine and may have to be long term. Healing can result in fibrosis which if severe may necessitate tracheostomy.

SARCOIDOSIS

Sarcoidosis is a slowly progressive disease with the larynx involved in fewer than 5% of cases. The laryngeal appearances very similar to those of TB and fungal infection with the supraglottic structures being primarily involved. The larynx is rarely involved without clinical or radiographic evidence of pulmonary involvement. Diagnosis is achieved by demonstration of microorganism-negative, non-necrotizing granulomas in a biopsy specimen with concurrent clinical evidence of multisystem involvement. Treatment is ensuring a safe airway, either by laser excision or tracheostomy, and systemic corticosteroids. Outpatient based steroid injection has been reported as being a viable alternative to both systemic steroids and operative intervention and may obviate the need for prolonged intubation or tracheostomy.[59]

GRANULOMATOSIS WITH POLYANGIITIS

Formerly called Wegener's granulomatosis, granulomatosos with polyangiitis (GPA) is a systemic disease affecting the upper and lower respiratory tract and kidneys with necrotizing granuloma and vasculitis. In up to 25% of patients the larynx is affected with the appearances of an acute inflammatory reaction initially. Eventually granulomatous ulcers develop, affecting primarily the subglottis in the long term. The anticytoplasmic autoantibody (C-ANCA) is specific with biopsy findings showing necrotizing granuloma and vasculitis. Treatment is with corticosteroids or cyclophosphamide. The airway will need appropriate expert management and is discussed in Chapter 76, Laryngeal stenosis in adults.

CANDIDIASIS

Laryngeal candidiasis is due to the opportunistic infection by the oropharyngeal *Candida albicans* in the larynx. It can be associated with immunocompromised patients, for example, due to cytotoxic chemotherapy or AIDS or more commonly in those patients who have received broad spectrum antibiotics, corticosteroids, or prolonged inhaled corticosteroid use, or have received radical radiotherapy. In the latter case the laryngeal findings are a diffuse erythema of the mucosa with an irregular friable white exudate which is superficial. In the immunocompromised patient, the inflammatory reaction is much deeper and possibly with ulceration. In the superficial case, there is a degree of dysphonia, but little else, treatment is with nystatin or fluconazole and is generally successful. In the deeply infected, and potentially ulcerated, there is pain on speaking and swallowing in addition to the dysphonia. More intensive treatment is required and in this case amphotericin B may be required.[60]

HISTOPLASMOSIS

This is a systemic mycotic disease caused by *Histoplasma capsulatum*. There are nodular granulomas which can affect the anterior larynx and epiglottis and may ulcerate. The clinical picture is very similar to TB and squamous cell carcinoma. The presentation is dysphonia with varying degrees of pain and dysphagia. Diagnosis is by culture of the organisms on Sabouraud's agar from the laryngeal ulcers and the complement fixation test. As laryngeal involvement effectively only occurs in patients with the disseminated form of the disease, a useful guide to the diagnosis is the presence of multiple small calcifications on chest CT scanning. Treatment is by Amphotericin B and securing a safe airway.[60]

BLASTOMYCOSIS

Fungal disease caused by *Blastomyces dermatiditis* which affects multiple organs. Those at increased risk are individuals in North America with prolonged exposure in wooded areas. Although skin is the next most commonly affected site after the lungs when the larynx is involved there are granular erythematous changes which may progress to ulceration and microabscesses, primarily affecting the vocal cords. The principal complaint is dysphonia and as with other chronic inflammatory disease there may be confusion with squamous cell carcinoma. Diagnosis is by identification of the fungus from the microabscesses. Treatment is by itraconazole or ketoconazole and amphotericin B in advanced cases.[60]

ACTINOMYCOSIS

Systemic chronic suppurative disease can be caused by the anaerobic bacteria *Actinomycoses bovis* or *Actinomycoses israeli*. The larynx becomes involved following involvement of the soft tissues of the cervical or submandibular regions, possibly with abscess or sinus tract formation, with progression into the paralaryngeal region. The larynx is diffusely erythematous, swollen and wooden. Diagnosis is by identification of classical 'sulphur granules' in the biopsy material and culture of the microorganisms. Treatment is with penicillin or tetracycline.[60, 61]

RHINOSCLEROMA

This is primarily a chronic infection of the nasal cavity caused by *Klebsiella rhinoscleromatis* but may involve the larynx. It has three stages,: first, catarrhal, with marked purulent rhinorrhoea, second, granulomatous, with small painless granulomas, and finally, sclerotic, with sclerosis of the larynx. This sequence has only been postulated and can take a varying amount of time to occur. The glottis and subglottis are the main areas which are involved. Diagnosis is by histological identification of Mikulicz's cells, foamy vacuolated histiocytes, and Russell bodies, birefingent red inclusions, and bacteriologically by culture of the organisms. Treatment is by aminoglcoside, cephalosporins or tetracycline.[62]

KEY POINTS

- Chronic infective processes in the larynx are uncommon.
- The laryngeal appearances in each process can be very similar.
- The laryngeal appearances can be confused with those of squamous cell carcinoma.

RADIATION INDUCED CHRONIC LARYNGITIS

One of the commonest causes of chronic laryngitis in a Head and Neck practice is radical radiotherapy for a head and neck malignancy. During a course of radical radiotherapy, there is an incrementally increasing acute inflammatory reaction which develops into chronic laryngitis. Although to a certain extent the reaction is dose dependent there is considerable variation in individual responses to the treatment. Modern radiation delivery techniques can reduce the radiation dose to the larynx. The treatment of the resulting chronic laryngitis is based on similar principles to that of non-specific laryngitis. There is a high prevalence of smokers in this group of patients. To both increase the efficacy of the radical radiotherapy and decrease the severity of the chronic laryngitis smoking cessation strategies should be employed. Voice therapy would intuitively seem to be appropriate, however, there is little evidence in favour of it. There has been significant debate regarding the role of GERD in the development of laryngeal cancer and whilst this has not been resolved acid suppression would seem appropriate in this group of patients.

CHRONIC LARYNGITIS IN AN IMMUNOCOMPROMISED HOST

Colonization and infection of the larynx with *Candida albicans* may occur in patients who become immunocompromised secondary to AIDS, treatment such as chemotherapy or long-term corticosteroids. The larynx has white patches on a friable erythematous mucosa and diagnosis is made by culture of the laryngeal plaques and secretions. Treatment is by nystatin, amphotericin B or fluconazole.

BEST CLINICAL PRACTICE

- ✓ Chronic laryngitis frequently has a multifactorial aetiology.
- ✓ The main aetiological factors are smoking, voice abuse and reflux disease.
- ✓ Following clinical diagnosis, treat with voice therapy, smoking cessation therapy and consider anti-reflux treatment.
- ✓ Surgery should be used for excision of discrete lesions and tissue sampling only.
- ✓ Any intervention for chronic laryngitis must be assessed by some form of outcome, preferably patient-centred.
- ✓ Chronic infectious processes in the larynx are rare and frequently mimic squamous cell carcinoma.

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CHAPTER 71

CONTEMPORARY MANAGEMENT OF LARYNGOTRACHEAL TRAUMA

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SEARCH STRATEGY

Data may be updated by a PubMed search using the keywords: larynx, trachea, trauma, regeneration and transplantation.

INTRODUCTION

The laryngotracheal region plays a pivotal role in providing the important functions of airway protection, swallow and phonation. Injury to structures in this region is diverse and rare. The complex anatomy of the larynx and cervical trachea means that if traumatic injury occurs, severe morbidity and mortality can result, therefore early, thorough assessment and management of these injuries are vital for achieving optimal patient outcomes. The aims of treatment are to maintain a safe airway and appropriate upper aerodigestive tract function in terms of both a safe swallow and voice.[1]

ANATOMY

The laryngotracheal complex consists of an intricate cartilaginous framework, which supports a variety of muscular and ligamentous soft tissue structures.[2] This complex can deflect significant traumatic force before being injured. The larynx is a midline neck structure protected anteriorly by the mandible and strap muscles, inferiorly by the sternum, posteriorly by the cervical spine and laterally by the sternocleidomastoid muscles. The rarity of laryngeal injuries is attributed to this anatomical configuration, which provides a degree of protection to the soft laryngeal structures.[3] However, substantial dysfunction can result when injury does occur. The larynx is divided into three subsites, namely, supraglottis, glottis and subglottis, which is continuous with the trachea inferiorly. The subglottic region, being the only complete cartilaginous ring structure, is the most sensitive and therefore most vulnerable even during trivial trauma.

EPIDEMIOLOGY AND AETIOLOGY OF LARYNGOTRACHEAL INJURY

Laryngotracheal injury is diverse, rare and potentially life-threatening. The reported incidence of injury in the literature varies from 1 in 5000 to 1 in 137 000 emergency department presentations.[1, 4–5] More than 2000 cases of mortality are attributed annually to neck trauma in the UK.[8] Females are more susceptible to laryngeal injury as they tend to have longer and more slender necks compared to their male counterparts. Despite this anatomical predisposition, close to 80% of traumatic laryngotracheal injuries occur in males, particularly in the second and third decades of life, owing to greater participation in violent sports and other physical activities.[5]

Injury to the laryngotracheal complex may involve damage to the bony, cartilaginous, neurovascular and soft tissue structures of the neck. The resultant damage is related to the mechanism of injury. However, central to all laryngotracheal injury is the potential for a compromised airway.

The mechanism of injury to the larynx may be external or internal, through inhalational or iatrogenic injuries. External traumatic injuries are classified as either blunt or penetrating. The former is most commonly a result of motor vehicle accidents, as well as other causes such as hanging, strangulation and contact sports,[9, 10] while the latter occurs primarily from gunshot wounds, followed by stab wounds.[10–12] With improved standards of road safety and increasing incidence of violent crimes in the community, the incidence of blunt laryngeal injuries has decreased, while that of penetrating injuries has increased.[9] Studies have attributed only around 5% of aerodigestive injuries to blunt trauma,[10, 13] while up to 15% of these injuries are due to penetrating trauma.[12]

Blunt injuries

Blunt injuries can be further classified into crush, clothesline and strangulation type injuries. The former type of blunt injury is sustained especially in motor vehicle accidents where the victim is thrust forwards with a hyper-extended neck, particularly in the absence of a seatbelt, exposing the larynx to anterior crushing forces (**Figure 71.1**). Clothesline injuries occur when there is high velocity impact of the larynx with a stationary object. For instance, when a rider of an unprotected vehicle such as a motorcycle or snowmobile hits a stationary object, a large amount of energy is imparted over a small area. This can lead to instant exsanguination from cricotracheal separation or a crushed larynx (**Figure 71.2**).[14] In strangulation-type blunt injuries, such as hanging or strangulation by a soft object, initial injury may be minor, but can subsequently lead to laryngeal oedema and a compromised airway.[15]

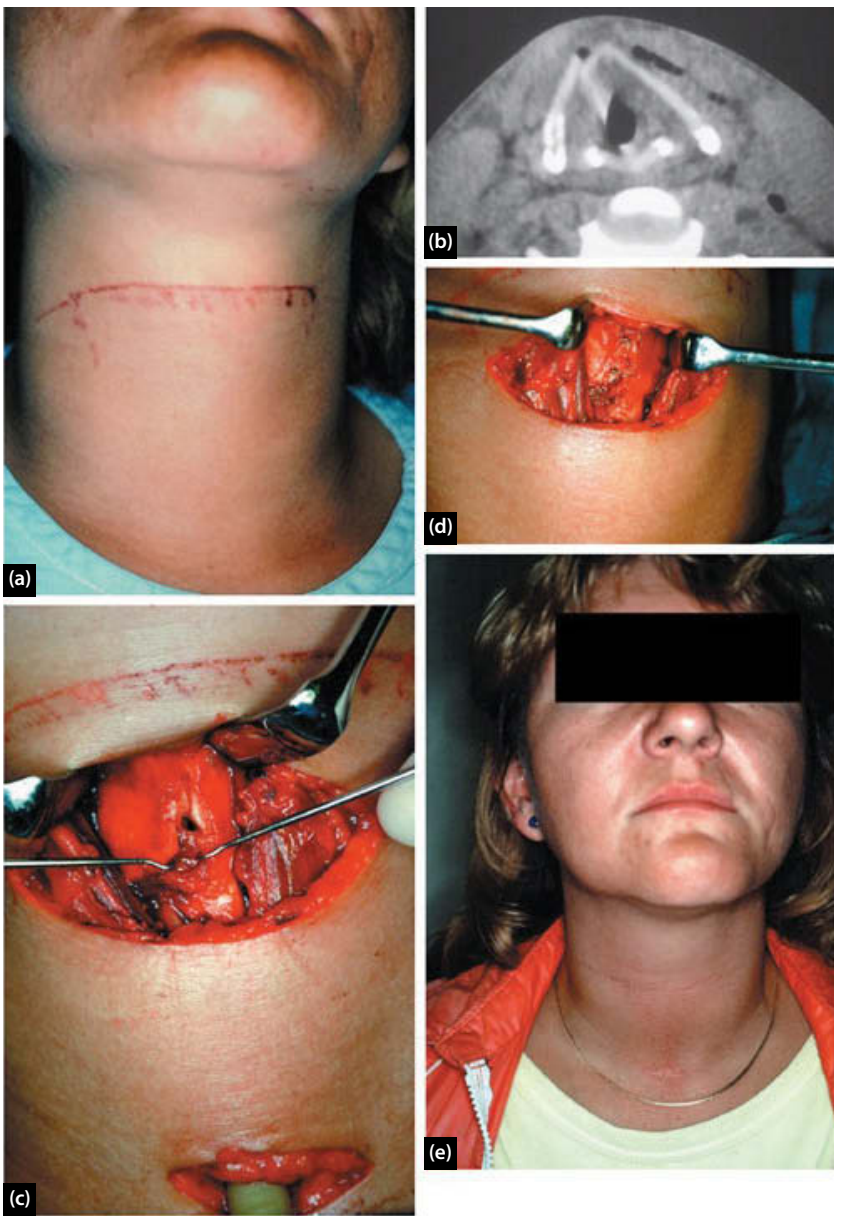


Figure 71.1 External laryngeal trauma from a motor vehicle accident. **(a)** Soft tissue findings of blunt trauma; **(b)** CT scan demonstrates paramedian thyroid cartilage fracture; **(c)** laryngeal fracture demonstrated during open exploration; **(d)** fracture reduction and repair with wire; **(e)** outcome at 1 year with good cosmetic and functional outcome.

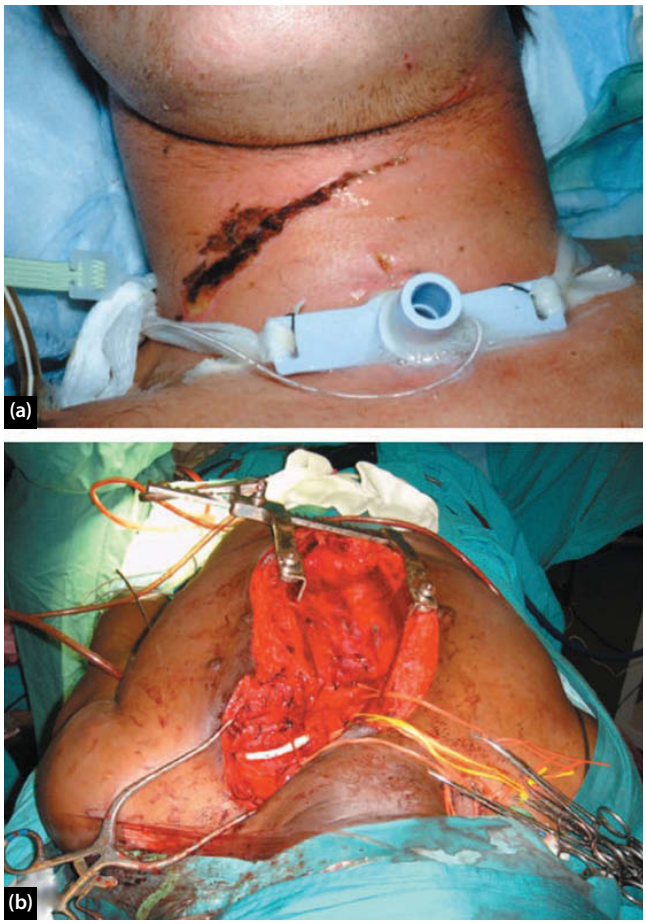


Figure 71.2 'Clothesline' injury with tracheal separation.

Penetrating injuries

Penetrating laryngotracheal injuries can cause varying degrees of damage depending on the location and the nature of the weapon used. Injury to neurovascular and soft tissue structures can result in variable amounts of oedema, inflammation, haemorrhage, scarring and anatomical disruption. Low velocity gunshot wounds, such as those sustained with hand guns, tend to cause moderate damage to the injured tissue, while high velocity gunshot wounds, such as those sustained with rifles, can cause wide-field damage of laryngeal tissue that may extend beyond the limit of necrotic tissue.[16] Unlike gunshot wounds, stab wounds from knives have a predictable course of injury that generally does not cause damage beyond the entry and exit path of the knife.

Inhalational injuries

Inhalational injuries to the larynx and trachea occur following inhalation of toxic gases, exposure to fires or ingestion of toxic substances. This leads to oedema of the airway, which tends to be self-limiting. However, ingestion of caustic substances can lead to full thickness airway burns, leading to significant morbidity. Inhalational injury involves transfer of high levels of thermal energy. Reflex closure of the glottis occurs as a protective mechanism to limit thermal injury to the supraglottic region. Early securement of the airway is important as subsequent and delayed upper aerodigestive tract oedema can occur in the hours following injury.

Iatrogenic injuries

Iatrogenic injuries to the laryngotracheal complex can occur following any airway management procedure such as during routine oro- or nasotracheal intubation, cricothyroidotomy or during elective operations such as laryngeal surgery, laryngoscopy or routine tracheostomy. Urgent tracheostomy, required for the management of an acute airway problem, is particularly prone to injury involving the upper aerodigestive tract, including the laryngotracheal complex. Studies have identified factors contributing to post-intubation injury, such as high cuff pressure, prolonged duration of intubation, use of large diameter endotracheal tubes as well as patient co-morbidities, such as diabetes and chronic obstructive pulmonary disease.[17–19] Following prolonged intubation, the associated inflammation can lead to sequelae of granulation and scarring with subglottic stenosis, vocal fold dysfunction or airway compromise.[20, 21]

PATHOPHYSIOLOGY OF LARYNGEAL TRAUMA

Tissues involved in laryngeal injury include mucosa, nerves (superior and recurrent laryngeal nerves), soft tissue (muscle – intrinsic and extrinsic muscles, ligaments, superficial lamina propria), cartilages (arytenoid, thyroid, and cricoid) and trachea (including trachealis muscle). In the acute situation, the main concern is the integrity of the airway, but in chronic laryngeal injury there are ensuing complications, which are variable and unpredictable. Healing by secondary intention can result in scarring, subluxation, and ankylosis of the arytenoids and cricoarytenoid joints. Fibrosis of the laryngeal muscles disrupts the mucosal wave, with the appearance of non-vibrating segments. There can be anterior and posterior glottic webbing, and supra- and sub-glottic scarring. Neural injury can lead to muscle palsy, and cartilage fractures may heal by secondary intention, resulting in unstable fractures, mal-union or non-union. Such chronic effects, unlike the acute situation, are slowly progressive and therefore not discernable at the outset (**Figure 71.3**).

Mature scar tissue in the background of oedema, haematoma and collapsed tissue (soft tissue or cartilage) can have variable impact. For example, in the posterior glottis, where granulations mature over time, the posterior vocal folds can be drawn together, leading to progressive shortness of breath and airway obstruction. Other sequelae include glottic incompetence, dysphonia, aspiration and dysphagia, but the chronicity of the changes allows time for glottic compensation. This is in contrast to the acute setting, where there is no time for the larynx to adapt.

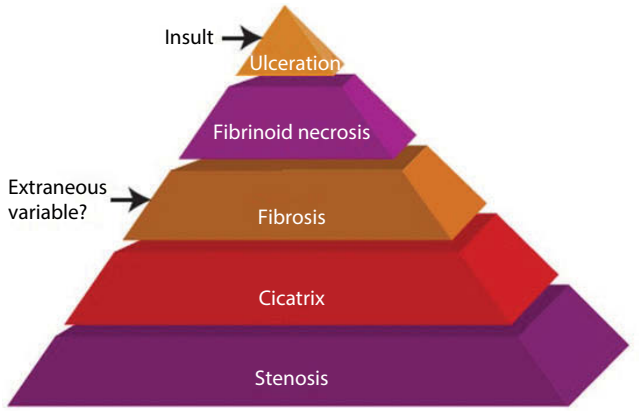


Figure 71.3 Pathophysiology in the development of a laryngeal stenosis.

BOX 71.1 Laryngotracheal injury classification by Trone et al[23]

Group 1:	Minor endolaryngeal haematoma without detectable fracture
Group 2:	Oedema, haematoma, minor mucosal disruption without exposed cartilage, non-displaced fractures noted on CT scan
Group 3:	Massive oedema, mucosal tears, exposed cartilage, fold immobility
Group 4:	As group 3, but with more than two fracture lines or massive trauma to laryngeal mucosa
Group 5:	Complete laryngotracheal separation (added by Fuhrman et al.[23])

CLASSIFICATION OF LARYNGEAL TRAUMA

A number of classification systems for traumatic laryngeal injury have been described. One such system by Fuhrman et al. classifies laryngotracheal injuries into five groups (**Box 71.1**).[22] This classification system is a modification of the previously proposed one by Trone et al, in which injury is divided into groups 1 to 4 only.[23] Group 1 comprises minor endolaryngeal haematoma without detectable fracture; group 2 injury involves oedema, haematoma, minor mucosal disruption, unexposed or undisplaced fractures; group 3 comprises injury where there is massive oedema, mucosal tears, exposed cartilage or vocal fold immobility; group 4 injury is as group 3 but with the addition of massive trauma to laryngeal mucosa or over two fracture lines; and group 5 injury is where there is complete laryngotracheal separation. These classification systems help to provide a unified approach to the assessment and management of laryngeal injuries.

Sequelae of major laryngeal trauma include stenoses at supraglottic, subglottic and/or posterior glottic levels. Classification of posterior glottic stenoses, described by Bogdasarian and Olson, is based on the structures involved (**Figure 71.4**).[24]

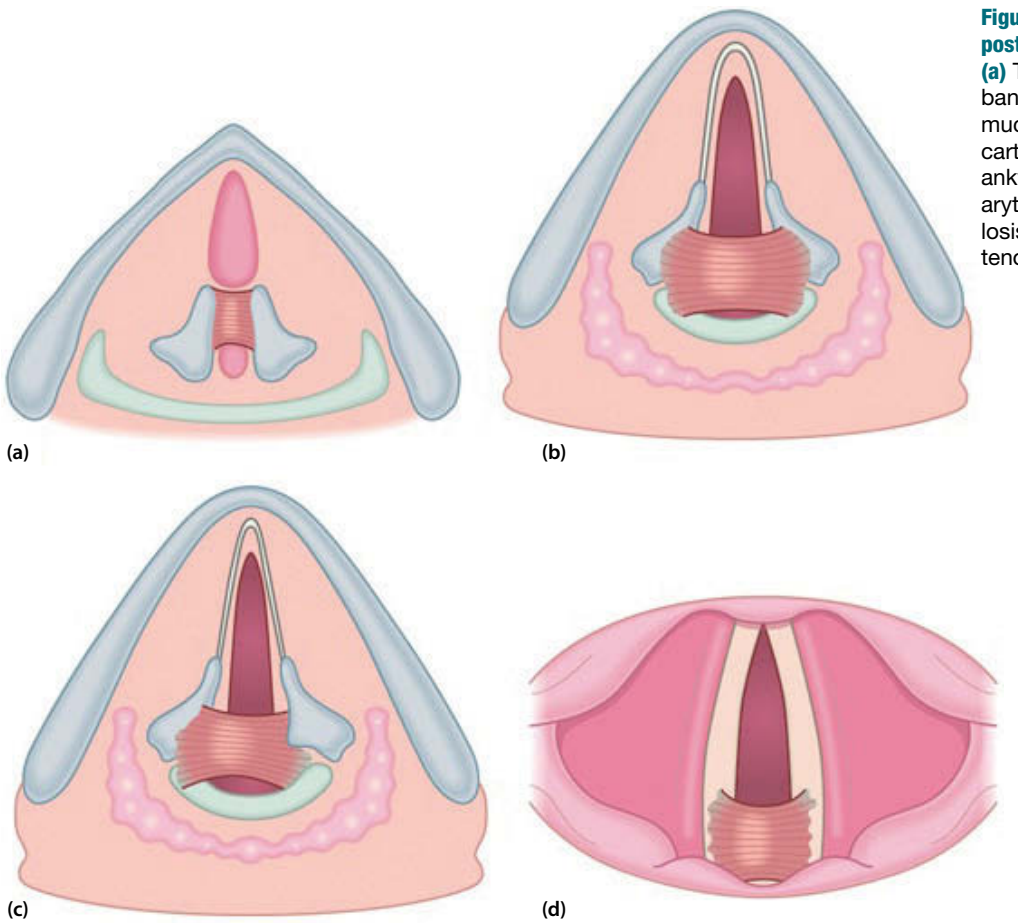


Figure 71.4 Classification of posterior glottic stenosis. **(a)** Type I, isolated interarytenoid band; **(b)** Type II, posterior glottic mucosal tunnel, but no arytenoid cartilage ankylosis; **(c)** Type III, ankylosis and immobility of one arytenoid joint; **(d)** Type IV, ankylosis and immobility of both arytenoid joints.

EVALUATION OF LARYNGOTRACHEAL TRAUMA

Timely assessment and management of laryngotracheal injury following the principles of advanced trauma and life support (ATLS) is essential.[25] It requires a multidisciplinary team approach including emergency physicians, trauma surgeons, otolaryngologists-head and neck surgeons, anaesthetists, radiologists, clinical nurse specialists and allied health professionals (**Figure 71.5**).

Signs and symptoms

Signs and symptoms associated with laryngeal injury vary with the mechanism and severity of injury. Laryngeal trauma may be part of multi-trauma involving other parts of the body and therefore must be assessed in a systematic manner. Urgent review of patients is vital as patients initially exhibiting only subtle symptoms and signs of upper aerodigestive tract dysfunction can progress to complete airway obstruction from worsening oedema.

The most common presenting symptoms include varying degrees of dysphonia and dyspnoea, followed by dysphagia, neck pain and haemoptysis. Patients with penetrating neck injuries can present with externally visible neck wounds, bleeding, expanding haematoma and/or bruising.[3, 6, 26] They may also be hypovolaemic, and in shock. Those with blunt injuries with no externally visible injury may have their injuries undetected for as long as 24–48 hours post-injury.[27, 28] The hallmark clinical signs of airway obstruction include stridor, increased respiratory rate, tachycardia, sweating and use of accessory muscles. The patient may be in shock, have ecchymosis in the skin of the neck, abrasions, open wounds, massive subcutaneous emphysema, expanding haematomas, tracheal deviation and cartilaginous and bony fractures.[28–30]

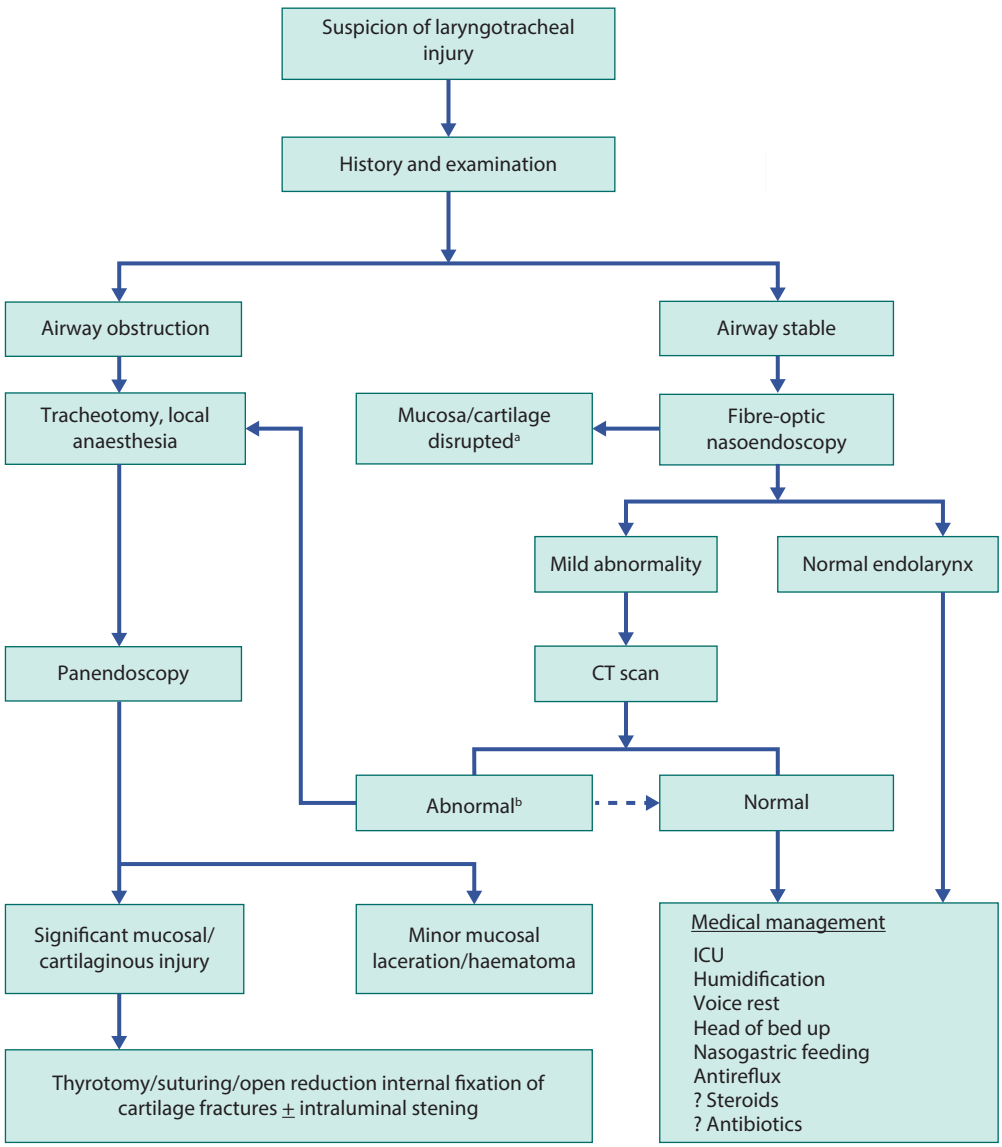


Figure 71.5 Management algorithm for patients presenting with laryngotracheal trauma.

AIRWAY MANAGEMENT

The primary goal in the initial evaluation and management of a patient with a suspected laryngotracheal injury, like any other presenting with a traumatic event, is to ensure the airway is adequately assessed and protected by the most senior and experienced medical staff available. Where there is any concern about impending airway obstruction, a safe airway must be established. Only after this has been achieved can the management of the trauma patient continue.

Once the patient is stabilized, a thorough history and examination including fibre-optic nasoendoscopy can be obtained to ascertain the mechanism, duration and extent of laryngeal injury and other concomitant injury. Fibre-optic nasoendoscopy can aid in assessing patency of the airway, vocal fold movement, presence of lacerations, haematomas and exposed cartilage.[31]

Options for acute management of the threatened airway include routine endotracheal intubation, fibre-optic awake intubation and tracheostomy under local anaesthetic. In emergent situations, cricothyroidotomy may be required, using a vertical incision to avoid the anterior jugular veins, allowing greater exposure of the airway.[28, 32] Blind endotracheal intubation must be avoided as it can lead to complete laryngotracheal separation in a partially transected airway held together by peri-tracheal soft tissue.[29] There is some controversy in the literature with regard to the best method to secure the airway. Several authors including Schaefer,[1] Fuhrman et al,[22] Hwang and Yeak[33] and Baron[34] recommend a tracheostomy under local anaesthetic as gold standard, while Gussack et al. recommend endotracheal intubation for airway management.[35] One argument for the former method is that a tracheostomy will enable examination of the site of laryngeal injury, as opposed to the latter technique, which may hinder further direct examination of the site of injury and may even cause iatrogenic aggravation of the existing injury.[6] Nevertheless, in experienced hands, there is adequate evidence in the literature to date supporting the safety of endotracheal intubation for airway management in laryngeal trauma.[6, 36]

When experienced personnel are unavailable, an emergency tracheostomy under local anaesthetic is recommended to secure the airway safely.[1, 37–39] This is ideally performed in a controlled environment as afforded by an operating theatre, where appropriate instrumentation, lighting and anaesthetic, surgical and nursing support are available. Tracheostomy under local anaesthetic is recommended to maintain spontaneous ventilation and patency of the upper aerodigestive tract until a definitive airway is established. However, in a struggling patient where this is not possible, an inhalational general anaesthetic with the highest possible inspired oxygen concentration may be administered. Muscle relaxants are contraindicated, as paralysis of spontaneous respiration and positive pressure ventilation can aggravate air leak and surgical emphysema, lead to loss of airway and result in respiratory arrest.[29] To avoid the area of laryngotracheal injury, the tracheostomy incision is ideally placed distal to the site of injury, slightly lower than usual. A horizontal incision midway between the cricoid cartilage and sternal notch is commonly used. Where a traumatic tracheotomy exists, Corneile et al. recommend the use of this wound to access the trachea as a means to provide greatest preservation of healthy trachea for repair and reconstruction.[28]

In paediatric laryngeal trauma, the preferred method of airway control consists of inhalational anaesthesia allowing for spontaneous ventilation, followed by securing the airway with rigid bronchoscopy and tracheostomy.[13, 40, 41] Cricothyroidotomy in this population is avoided as it may not provide adequate exposure, and can potentially compound the existing injury.[13, 40, 41]

Once the airway is established, further operative evaluation and exploration of the laryngotracheal injury can occur. Microlaryngoscopy, oesophagoscopy and bronchoscopy are essential aids to assess extent of injury, and photo-documentation can also be obtained simultaneously. There is some controversy with regard to timing of operative exploration once the airway has been established. Whilst some authors recommend delaying exploration until oedema at the site of injury has subsided,[42, 43] the consensus recommendation is exploration within 24 hours of injury.[1, 6, 44]

IMAGING

Following stabilization of the airway, computerized tomography (CT) with three-dimensional reconstruction and magnetic resonance imaging (MRI) are gold standard radiological modalities to assess the larynx and its framework. CT scans can provide useful information about the anatomy, and aid in management decisions.[12] The findings to look for in the setting of laryngotracheal trauma include cartilage fractures, haematoma, oedema, cricoarytenoid joint dislocation or subluxation, extra-tracheal subcutaneous air and airway stenosis. It is used in conjunction with, rather than as a replacement for, operative exploration.

Furthermore, CT and MRI can identify missed laryngeal injuries in symptomatic patients with chronic sequelae.[45] CT angiography is very important in cases of penetrating trauma, especially involving neck zones 1 and 3, where information on the location and trajectory of foreign bodies, such as bullets or shrapnel, and integrity of vascular structures must be obtained.[46]

MANAGEMENT OF LARYNGOTRACHEAL INJURIES

The management of laryngotracheal injuries may be non-surgical or surgical depending on the type and extent of injury and follows a thorough assessment of the patient.

Non-operative approach

Non-operative management options are determined by the type and extent of injury, and coexisting illnesses of the patient. Airway stability is integral to non-operative

management and assumes protection by the patient's own reflexes or by an endotracheal tube.

Atkins et al.[12] and Bisase et al.[47] recommend such an approach to management of patients with group 1 and 2 type traumatic laryngeal trauma. These injuries include minor mucosal lacerations without exposed cartilage or bone and minor hematomas. Bent et al,[4] Schaefer[1] and Close[15] also recommend such an approach in patients with undisplaced single fractures of the laryngeal cartilaginous framework. The non-operative management of these patients involves admission to an intensive care unit for airway monitoring for at least 24 hours and treatment with constant humidification, head elevation, nil by mouth and voice rest. Some patients may also require endotracheal intubation if there is concern about their ability to maintain their airway. Intubation also aids in performing a panendoscopy to rule out injury to other structures in the upper aerodigestive tract. If this examination is unremarkable, the patient can be safely managed using a closely monitored non-operative approach.

Blockade of gastric acid reflux is recommended to prevent further irritation of the injured laryngeal mucosa and laryngeal stenosis.[12, 48] The effectiveness of corticosteroids in reducing soft tissue oedema in laryngeal trauma remains unclear due to lack of supporting evidence. Further, if used, they must be given within a few hours of the injury. Similarly, the use of antibiotics in non-operative management of laryngeal trauma is also controversial. Some authors suggest that intravenous penicillin or cephalosporin can help reduce development of granulation tissue and potential infection following panendoscopy.[12, 49, 50]

Operative approach

Surgical intervention is required in patients in whom non-operative management options are unsuccessful in improving airway function, or those who continue to deteriorate despite these measures. Surgery is aimed at airway preservation, prevention of secondary sequelae of healing and restoration of function via repair of endolaryngeal and other concomitant injuries such as neurovascular damage, or thoracic injuries, and stabilization of fractures of the laryngeal framework. The type, timing and severity of injury and patient comorbidities, determine the surgical management, as detailed here.

ENDOSCOPIC

If the anaesthetist fails to intubate using an intubating laryngoscope, an anterior commissure scope can be passed by the otolaryngology head and neck surgeon to facilitate careful placement of a microlaryngoscopy tube. Once the airway is secured, examination of the laryngotracheal complex can be performed endoscopically using a variety of straight and angled telescopes. Haematomas of the vocal folds can be aspirated, and damaged folds re-approximated by suturing. Stents can be placed endoscopically in the acute situation to support the laryngeal framework and lumen, reduce the likelihood of adhesions, and maintain the structure of the anterior commissure for voice preservation, particularly if there is extensive mucosal disruption, or comminuted fracture(s). Rigid oesophagoscopy should also be performed acutely to exclude any injury to the integrity of the oesophagus.

Chronic sequelae of laryngeal trauma can be managed endoscopically. Cold steel or laser division of supraglottic webs, with or without an epiglottopexy, can be performed. Similarly, glottic adhesions can be divided and, if necessary, a cordotomy, cordectomy or arytenoidectomy undertaken. As in the acute situation, stents can be placed for the reasons described above.[51] Silastic keel placement, for 1–2 weeks, combined with vocal fold mucosal suturing can be used to treat post-traumatic laryngeal webs. Mucosal suturing of the vocal fold reduces raw surface exposure, and ultimately avoids long-term glottic stenting, laryngofissure, and requirement for tracheostomy.[52] Mitomycin-C can be injected to reduce fibrosis.[53–57] There is evidence in human and animal studies for the use of Mitomycin-C, which inhibits fibroblast proliferation by cross-linking DNA, and 5-fluorouracil/triamcinolone at the time of ablation of stenosis, or dilatation to inhibit restenosis,[53–57] although there is still some controversy regarding their effectiveness.

A bulking agent, such as hyaluronic acid, can be administered in an endoscopic injection thyroplasty procedure, to a vocal fold, injured from previous intubation or gastroscopy injury.[58] Endoscopic balloon or bougie dilatation, usually a temporizing option, can be performed with the adjunct of botulinum toxin injection to relax a stenosed cricopharyngeus.[59]

Endoscopic management of laryngotracheal stenosis is thought to be appropriate for patients whose injury does not involve the cartilage. Balloon dilatation can be used initially, but since the introduction of carbon dioxide (CO_2) lasers, a variety of endoscopic management techniques have evolved.[60] These include the neodynium-doped yttrium aluminium garnet (Nd:YAG) and microscope-mounted CO_2 laser.[61] Recently, CO_2 ablation via awake flexible bronchoscopy has been described.[62, 63]

OPEN

An open approach to traumatic laryngotracheal injury is recommended for patients with group 3 and 4 injuries, and a subset of those with group 2 injury who have minimally or non-displaced fractures. Emergent tracheostomy, surgical exploration and immediate repair is the standard of care in all patients in whom complete cricotracheal separation (group 5 injury) is suspected (**Figures 71.6a–71.6d**). In addition, the presence of concomitant neurovascular, thoracic or abdominal injuries, and individual patient factors, should tailor the surgical plan. There is some controversy regarding the timing of surgical intervention in those patients with group 3 and 4 injuries; some studies recommend surgery after soft tissue oedema has settled whilst others recommend surgical exploration early (within 24–48 hours) to avoid voice and airway dysfunction in the long term.[64] The consensus recommendation is exploration within 24 hours of injury.[6, 9, 44]

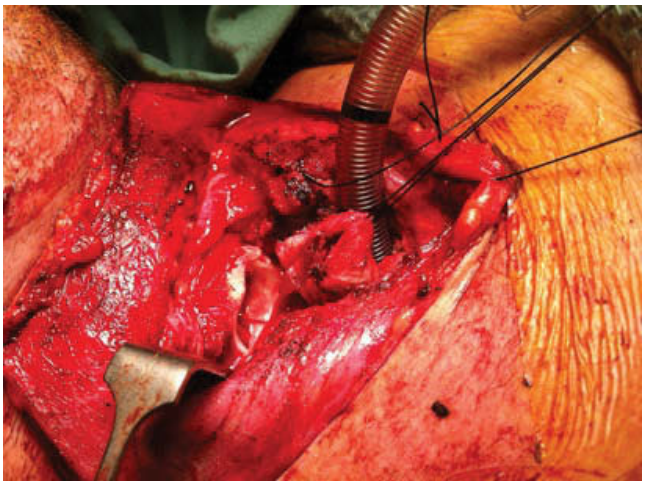


Figure 71.6a Patient presenting following a non-restraint motor vehicle accident with multi-system trauma including complete cricotracheal separation and multiple fractures of the cricoid cartilage.

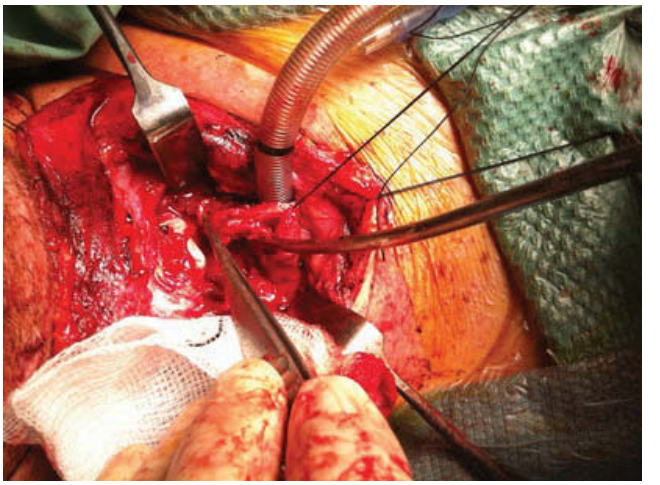


Figure 71.6b Forceps point to avulsed left recurrent laryngeal nerve.

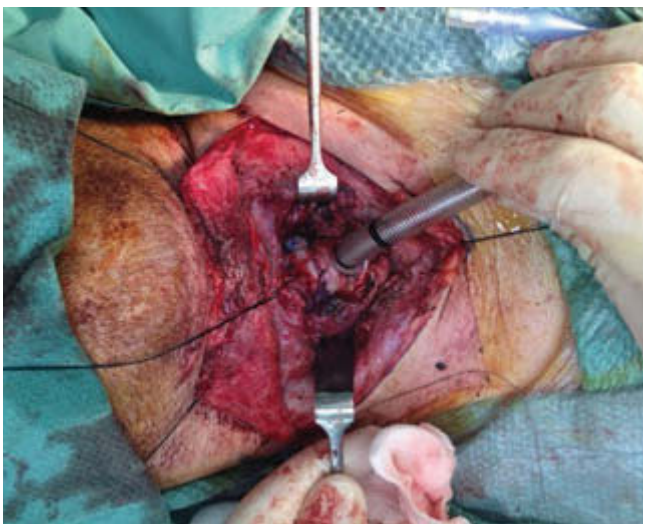


Figure 71.6c Repair was carried out in the operating theatre after tracheostomy was performed. The cricoid cartilage was repaired using non-absorbable sutures. Primary cricotracheal anastomosis was performed using vicryl.

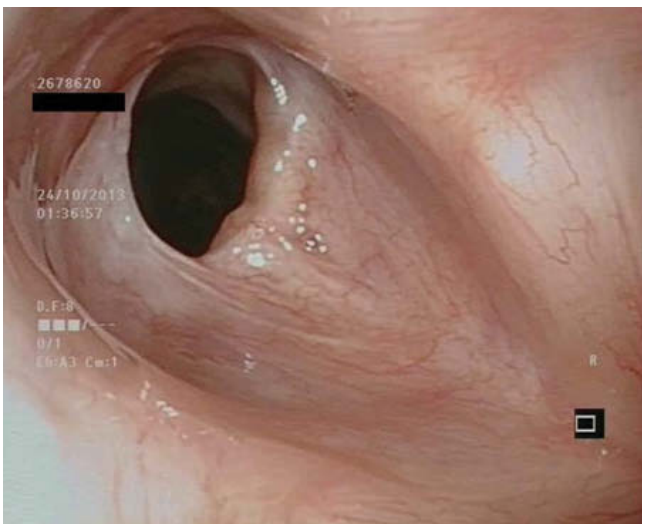


Figure 71.6d Appearance of larynx 1 year post-operatively, demonstrating a patent airway, despite the anterior glottic web and bilateral vocal fold palsies.

An open approach is reserved acutely for displaced or comminuted laryngeal fractures that are deemed unstable due to muscular forces, and therefore unsuitable for endoscopic repair.[65] Neural repair is rarely performed in the acute setting, unless iatrogenic, for instance in thyroidectomy. Suitable cable graft nerves include ansa cervicalis, great auricular nerve and sural nerve.

An open approach is used less commonly in the chronic situation, and usually addresses functional deficits relating to airway, voice and swallow. Cricotracheal resection may be performed for chronic subglottic stenosis, type I Ishiki open thyroplasty to medialize a paralyzed vocal fold, and cricopharyngeal myotomy for cricopharyngeal stenosis.

The open surgical technique of managing laryngotracheal stenosis is employed when cartilage integrity is not preserved or where repair is refractory to endoscopic techniques. A number of open approaches, including single and double stage reconstruction, cricotracheal resection (**Figure 71.7**), use of stents, and anterior and posterior grafting, have been described. The type of approach used is selected based on pre-operative evaluation of the stenotic region and patient comorbidities, and is discussed in detail in Chapter 76, Laryngeal stenosis in adults. Simple circumferential resection with primary anastomosis provides excellent outcome in suitably selected patients.[64, 65] Stenosis that is at a distance greater than 1.5 cm from the inferior aspect of the vocal folds is considered safe for resection with primary anastomosis.[66] Pearson et al. have suggested that up to half the trachea can be resected and managed with primary anastomosis.[67] Macchiarini et al. recommend resection of no more than 4 cm of stenosed trachea to avoid anastomotic tension and failure.[68] To achieve optimal outcome, patients must be optimized preoperatively in terms of treating their comorbidities, such

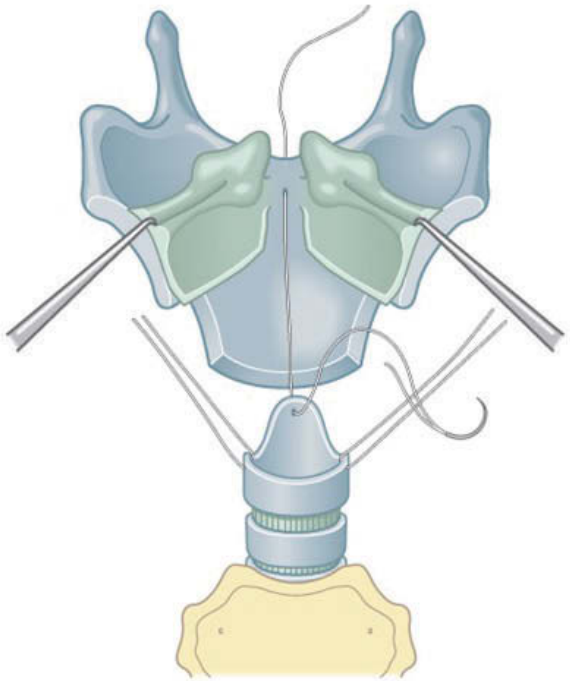
as those with immunosuppressive conditions (e.g. diabetes, vascular disease) or those taking immunosuppressive drugs. In addition, complete resection of the stenotic tissue and provision of adequate airway support post-operatively are essential for a successful outcome.

With regard to surgical approach, the patient is positioned supine with a shoulder roll to extend the cervical spine slightly. Typically, the upper aerodigestive tract is approached through a horizontal collar type incision at the level of the cricothyroid membrane, but the traumatic entry incision may provide an alternative means of entry.[40] Through this incision, superior and inferior subplastysmal flaps are raised, followed by division of the strap muscles and thyroid isthmus to maximize exposure of the laryngotracheal complex.[12, 40] Where more distal injuries are present, a partial sternotomy or right thoracotomy can be performed via this incision.[69] A laryngofissure (or midline thyrotomy) approach will expose the endolarynx, and avoids injury to the recurrent laryngeal nerve.[39, 70, 71] A laryngofissure enables debridement of contaminated tissue and removal of foreign material, repair of mucosal lacerations, and areas of denuded cartilage to be covered with mucosal flaps or skin grafts.[40, 71] Vocal folds can be repositioned and sutured in place, if necessary, using a dissolvable fine suture material.[12] This may also require an arytenopexy.[72]

All laryngeal fractures must be identified, reduced and stabilized. Repair of these fractures involves raising the perichondrial layer and suturing it with non-absorbable sutures. In addition to simple suturing, wiring the fractured cartilage segments and internal fixation with adaptation metal plates, when available, are the most contemporary methods used to stabilize laryngeal fractures.[73, 74] Alloy metal miniplates with self-tapping screws were traditionally used to bridge any fracture line, and enable the laryngeal framework to be restored as best as possible. An alternative to metal plates are malleable, non-metallic biodegradable plates, such as poly-L-lactic-acid-polyglycolic-acid,[75, 76] which slowly resorb over 1.5 to 3 years.

Avulsion injuries to the anterior commissure can also be repaired by careful suturing of the anterior aspect of the true vocal folds to the outer thyroid cartilage perichondrium.[9] Reconstruction options where there is loss of cartilage vary from the use of local muscle flaps, using either the strap muscles or parts of the sternocleidomastoid, to filling the defect, to the use of free grafts for more extensive cartilage loss, most commonly from the rib.[77] A covering tracheostomy, 2–3 tracheal rings below the site of repair, is placed for ventilation at the time of repair and to ensure a safe airway in the post-operative period.

The use of stents in laryngotracheal reconstruction is recommended where there is disruption of the anterior commissure anatomy, extensive mucosal trauma and comminuted fractures with significant damage to the laryngotracheal complex (**Figure 71.8**). Ideally these stents should be softer and more inert than hard intraluminal stents, and inserted for the shortest time possible, to avoid growth of granulation tissue.[78, 79] Schaefer recommends that they be secured in the larynx by double



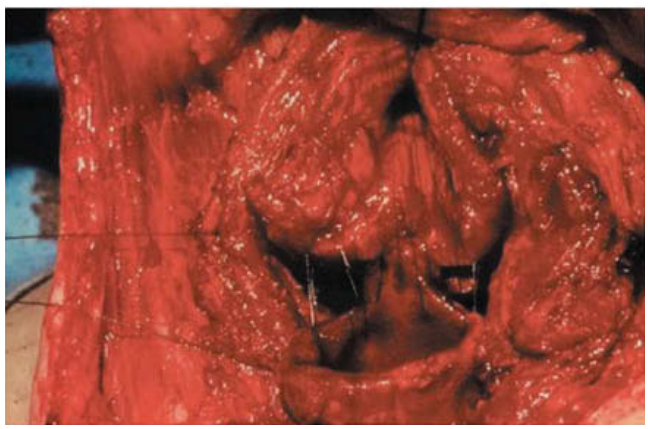


Figure 71.7 High cricotracheal separation with laryngofissure and repair using a membranous tracheal mucosa flap.

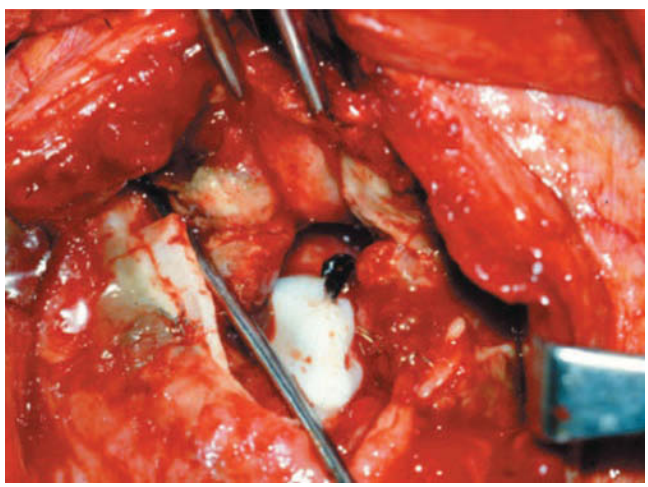


Figure 71.8 Thyroid and cricoid cartilage fracture with placement of Montgomery laryngeal stent.

sutures, and closed at the superior end, to avoid aspiration of fluids via the stent lumen.[9] In addition to a rolled silastic sheet and moulded Portex tracheostomy tube stent, a variety of newer laryngeal stents are available, which are softer and more inert. These include the Montgomery laryngeal stent, Montgomery T-tube, Aboulker stent, Eliachar laryngotracheal stent and the LT-Mold stent. However, regardless of the type of stent used, the decision to stent is made based on the need to stabilize the airway versus the potential for further laryngeal injury and infection from stenting.[80]

Repair of laryngeal nerve injury is still largely at an experimental stage. Recently, a rat model for the characterization of laryngeal function, routes of innervation, and sources of reinnervation following recurrent laryngeal nerve (RLN) resection has been developed.[81] In another rat model, the intact superior laryngeal nerve (SLN) has been used to investigate the reinnervation process of the posterior cricoarytenoid (PCA) muscle following RLN injury.[82] In this, PCA reinnervation was assessed by retrograde double-tracing techniques. The PCA was shown to receive dual innervation from both laryngeal nerves, even in the uninjured system. Following RLN injury, functionally significant collateral reinnervation originated from intact SLN fibres, mainly due to intra-muscular growth rather than by recruitment of more motor neurons.

FUTURE DIRECTIONS

Laryngeal tissue engineering

In the past decade, research into tissue engineering for laryngeal reconstruction has been growing, in particular for scarred vocal folds following trauma. This technique is still in its infancy, however, in terms of clinical application. Tissue engineering methods include the use of specific growth factors and mesenchymal stem cells (MSCs).[83]

Certain growth factors, such as basic fibroblast growth factor (bFGF), are already in use for vocal fold regeneration for cases of vocal fold atrophy. bFGF has been used to treat presbyphonia. Vocal fold atrophy was shown to improve at 1 week post-injection. Aerodynamic and acoustic parameters also demonstrated improvements, which were maintained up to 3 months.[84]

Transforming growth factor (TGF)-β3 reduces collagen synthesis and subsequent scar formation. This has been demonstrated experimentally in beagle dogs in which the lamina propria of the vocal folds was injected either with TGF-β3 or saline prior to the folds being injured by stripping of the lamina propria.[85] When larynxes were harvested at 6 months, histological analysis showed that TGF-β3 had suppressed granulation-tissue formation and scarring. Collagen distribution was well organized and less dense in TGF-β3-treated vocal folds compared to saline-treated vocal folds. TGF-β3-treated vocal folds demonstrated significantly better vibratory function.

Another growth factor, granulocyte-macrophage colony-stimulating factor (GM-CSF) assists in epithelial wound healing, and has recently been applied experimentally to promote tissue repair. In a study of vocal fold healing following injury to the vocal folds of New Zealand white rabbits, either GM-CSF or saline as a control was injected into their vocal folds.[86] The GM-CSF-treated vocal folds showed reduced collagen type I and fibronectin deposition in comparison to the saline-injected controls. Mucosal waves in the GM-CSF cohort exhibited significant improvement compared to the phosphate buffered saline cohort. In the *in vitro* arm of the study, human vocal fold fibroblasts (hVFFs) were cultured with GM-CSF. GM-CSF prevented TGF-β1-induced collagen synthesis by hVFFs, thereby reducing scar formation. The expressions of extracellular matrix-related enzymes and growth factors hyaluronan synthase-2, tropoelastin, matrix metalloproteinase-1, hepatocyte growth factor (HGF), and c-Met mRNA were significantly increased by GM-CSF. These findings suggest that GM-CSF offers therapeutic potential for the remodelling and regeneration of vocal folds following injury.

The application of growth factors could have a refractory effect if used inappropriately in terms of dosage, route and time of application. Therefore their application is in the process of being refined for safe and large-scale use in the near future.[83]

The use of MSCs has emerged as a potential therapy in the future for head and neck reconstruction. MSCs can differentiate along a specific cell lineage but also have the capacity for self-regeneration. However, this regenerative ability may be a double-edged sword due to the possibility of malignant transformation.[87, 88] MSCs are originally derived from adipose tissue but have also been derived from bone marrow and thymic progenitors.[89] These MSCs appear promising for reconstruction based on *in vivo* and *in vitro* studies in animals, due to their continuous circulation in the peripheral blood, ability to migrate to sites of injury to stimulate resident stem cell proliferation and secretion of growth factors,[90] and their differentiation into myofibroblasts and fibroblasts.[91]

An animal model study of green fluorescent protein-labelled MSCs in rats showed that MSCs were distributed throughout the vocal fold from day 1 following vocal fold injury, and that there was up-regulation of HGF compared with control-treated folds.[92] A suitable scaffold is necessary for MSC implantation. A subsequent *in vitro* study examined the role of Terudermis, an atelocollagen sponge derived from calf dermis with large pores that enable cellular entry.[93] It demonstrated adhesion of MSCs to Terudermis, with positivity for the cell adhesion molecules vimentin, desmin, fibronectin and fspl within the scaffold, showing the importance of Terudermis as a scaffold for MSCs in the treatment of scarred vocal folds. These results have been borne out by an *in vivo* study, which examined the effect of injecting MSCs that had been incubated in a scaffold of atelocollagen into beagle dog vocal folds.[87] Histological analysis

showed a greater degree of regeneration in those vocal folds that had been injected with the combined scaffold of MSCs and atelocollagen compared with atelocollagen alone.

Similar results for vocal fold healing have been obtained with an injectable hyaluronic acid/mildly cross-linked alginate (HA/ALG) hydrogel scaffold containing human adipose-derived MSCs (hAdMSCs).[94] Histological evaluation demonstrated that treatment with hAdMSCs in HA/ALG hydrogel produced more favourable changes to the extracellular matrix than hAdMSCs alone. In particular, the combination of hAdMSCs in HA/ALG hydrogel prevented excessive deposition of collagen type I and increased HGF activity in regenerating vocal folds. The combination treatment also resulted in functional improvements in viscoelastic properties.

These results highlight the potential therapeutic role of MSCs, held within a suitable collagen scaffold, in the regeneration of vocal folds that have been scarred by trauma, and show the importance of up-regulation of growth factors such as HGF and other cell adhesion molecules to produce a robust extracellular matrix for vocal fold regeneration.

Jungebluth et al. described successful transplantation of a bioengineered trachea using autologous bone marrow-derived MSCs, seeded on a bioartificial nanocomposite.[95] Due to the complexity of laryngeal anatomy and physiology, concerns about the neoplastic potential of MSCs, and their appropriate and safe harvesting and application, MSCs are, in some respects, more suited to bioengineered tracheal transplantation, where the tissue anatomy is more simplistic. Currently the role of MSCs and growth factors is limited to regeneration of vocal folds that have been scarred by trauma, rather than to injuries affecting the intricacies of the laryngeal framework.

Laryngotracheal transplantation

The concept of laryngotracheal transplantation has been present for decades; however, the difficult anatomy and microvascular structure of the region, as well as the necessity for prolonged inhibition of T-cell activation,[96] have posed some hurdles. The first attempt at human transplantation, whereby a partial laryngectomy was undertaken, was in 1969.[97] Following this, in 1998, a successful total laryngeal transplant was performed, which has survived at least 12 years later, despite issues of chronic rejection.[98, 99] A further 13 cases of laryngeal transplants have been reported from Colombia but their long-term reports are still awaited.[100] More recently, Farwell et al. have provided an account of a successful, modified transplant of a larynx with long segment of trachea.[101] They were able to revascularize successfully, and reinnervate parts of the transplant selectively, with patient recovery at 3 months showing no evidence of rejection.

Porcine laryngeal transplantation has been described, with patent airways and restoration of swallowing at 1 week, and no evidence of ischaemia-perfusion injury in major histocompatibility complex-matched pigs.[102, 103] More recently, staged laryngeal allotransplantation has been described in beagle dogs.[104]

It is evident that the idea of laryngeal transplantation is still in its infancy. It is only suitable for a subset of people who have endured severe trauma, requiring laryngectomy, and carries with it the challenges of a prolonged recovery and lifelong immunosuppression. With advances in transplant technology, this could become a more viable option in future. There are inevitable issues concerning patient selection, reinnervation, immunosuppression and cost-benefit to be overcome.[105]

CONCLUSION

Injuries to the laryngotracheal region are diverse, relatively rare and potentially life-threatening. The key to successful outcomes in terms of survival, airway, a safe swallow and voice is early recognition, assessment and state of the art management of these injuries. Advances in imaging techniques and fibre-optic endoscopy have aided improved evaluation of these patients. Furthermore, a multidisciplinary team approach is essential for managing laryngotracheal injuries and, depending on patient, injury and treatment-specific factors, may involve operative or non-operative techniques. The use of bioengineered laryngeal tissue and laryngeal transplantation may become viable options in the future, to provide improved functional outcome for patients.

KEY POINTS

- The aetiology of trauma to the larynx and trachea is wide-ranging, resulting in complex and potentially life-threatening injuries.
- A multidisciplinary approach in a centre with expertise in complex head and neck disease will enable airway protection and assessment of the extent of injury, to determine the best management and timing of any potential operative intervention.
- Chronic upper aerodigestive tract dysfunction is a likely sequela and requires prolonged rehabilitation.
- Laryngeal tissue engineering is an expanding field which has provided a foundation for transplantation in animal models and humans.

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CHAPTER 72

UPPER AIRWAY OBSTRUCTION AND TRACHEOSTOMY

Paul Pracy and Peter Conboy

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SEARCH STRATEGY

Data in this chapter may be updated by a Medline search using the keywords: upper airway obstruction, tracheostomy and focusing on diagnosis and management. The evidence in this chapter is mainly level 3/4 with some level 2 evidence. The clinical recommendations are predominantly B and C.

INTRODUCTION

The scenario of a patient presenting with upper airway obstruction is one of the most challenging that a doctor can be faced with. This chapter aims to review the options available for the management of upper airway obstruction. The primary goal is to secure a safe airway with minimal invasion appropriate to the clinical scenario.

The causes of upper airway obstruction are varied and some are immediately apparent whilst others are subtle. Penetrating and blunt trauma to the head and neck region with acute airway compromise are particularly difficult situations to manage, both in the pre-hospital setting and on arrival in hospital. Infections of the upper airway that may result in compromise include peritonsillar abscess, parapharyngeal space abscess, retropharyngeal abscess and epiglottitis. Hypertrophy and neoplasia of lymphoid tissue in the tonsils and tongue base typically evolves more slowly. Primary malignancy of the head and neck mucosal surfaces may also present with upper airway obstruction. Airway compromise associated with paralysis of the vocal cords and foreign body obstruction occurs far less commonly in adults.

There is potential for conflict between the considerations of the safe and secure airway and minimizing the intervention to be undertaken. This risk management problem is more apparent in the acute setting where comprehensive assessment of the ill patient is difficult and other coexisting medical problems may not be known.

SYMPTOMS AND SIGNS

In the absence of acute trauma to the upper airway, the symptoms described are often non-specific and include dyspnoea, cough and voice change. It should be noted that these symptoms might also indicate lower airway disease. Given the dual purpose of the upper aerodigestive tract, it is not surprising that these primary airway symptoms may coexist with dysphagia, pain on swallowing or referred otalgia. Noisy breathing implies turbulent airflow and airway compromise. Progression of this symptom heralds impending complete airway obstruction.

Stridor and stertor

Noisy breathing tends to have different characteristics depending on the level of upper airway obstruction. Stertor is defined as a heavy snoring sound that is low-pitched and indicates obstruction or collapse in the pharyngeal airway. Stridor is a high-pitched noise that can be mistaken for wheeze. Stridor arises from compromise of the airway at the level of the larynx and trachea and is generated by turbulent airflow. Stridor can be inspiratory, expiratory or biphasic (**Box 72.1**). Careful clinical assessment of timing of the stridor helps to localize the level of obstruction.

The extrathoracic airway has a tendency to collapse on inspiration and to expand on expiration. A reduction in the airway diameter at this level is therefore more

BOX 72.1 Stridor and level of airway obstruction

- **Inspiratory:** obstruction at and above the glottic larynx
- **Expiratory:** obstruction of the intrathoracic airway
- **Biphasic:** obstruction associated with subglottic and tracheal lesions

apparent on inspiration. This is the case with pharyngeal narrowing, or compromise of the supraglottis and glottis by a pedunculated lesion being sucked into the airway on inspiration and blown clear on expiration (producing a 'ball-valve' effect). The opposite applies to the intrathoracic airway where increased negative intrapleural pressure in inspiration leads to an increase in the airway diameter. During expiration, there is increased extrinsic pressure on the airway that exacerbates any narrowing. The subglottis and trachea is usually immune to the pressure fluctuations arising from the respiratory cycle due to cartilaginous support and therefore stridor at these levels is typically biphasic.

Increased work of breathing is also indicated by suprasternal, intercostal and subcostal recession as well as nasal flaring. This is accompanied by increased use of the accessory muscles of respiration.

Voice change

Changes in the vocal quality arise from impaired vocal fold vibration or altered vocal cord movement. Hoarseness results from many types of injuries and may signal oedema, mucosal disruption, cartilaginous injury and impaired vocal cord movement. Typically, the greater the degree of hoarseness, the greater the severity of laryngeal injury. Aphonia is often associated with severe injury. Voice change can also indicate the presence of a lesion altering the normal vocal fold structure producing impaired vibration.

Drooling and bleeding

Drooling is a symptom that indicates either pharyngeal or oesophageal obstruction or the avoidance of swallowing due to the presence of significant pain brought on by deglutition. This may arise from trauma or infection. Bleeding indicates mucosal trauma or exposure of a vascular structure by an invasive lesion. In the case of trauma, depending on the severity it may not be possible to identify the level of bleeding and it should be remembered that there may be more than one source.

Fractures and subcutaneous emphysema

Blunt trauma to the head and neck area may result in fractures of the maxilla, mandible, larynx or trachea. Significant pharyngeal trauma and fractures of the laryngeal skeleton or trachea may give rise to surgical emphysema. This may add to the extrinsic compression and independently worsen the upper airway obstruction.

MANAGEMENT

Assessment

The importance of the initial assessment and immediate management of the patient with upper airway obstruction cannot be underestimated. In resuscitation scenarios, the principle of an ABCDE approach is adopted. The airway (with appropriate consideration of the cervical spine in trauma) is always the first step in patient management, followed by consideration of breathing and circulation. This leads on to a neurological assessment and then a general evaluation. The general evaluation includes a determination of the extent and severity of the neck/chest injury.

The patient must be examined to exclude or address any immediately reversible causes of airway obstruction. Where any concern exists regarding the immediate safety of the airway, it should be secured by the least invasive technique that the attending clinician is capable of without delay. In trauma cases with possible cervical spine injury, appropriate imaging of the spine is required and in cases of uncertainty cervical spine protection must also be considered.

Whilst the assessment of the critically ill patient needs to be rapid it must also be systematic and thorough. Careful eliciting of the symptoms and signs will usually provide sufficient information on how to proceed. Where the airway is sufficiently stable but no cause for the airway compromise has been identified, the examination should include a transnasal fibre-optic endoscopy. This is generally well tolerated and provides vital information as to the site, degree and nature of the obstruction. It permits assessment of the state of the mucosa (presence of oedema, lacerations, blood) the appearance of the laryngeal structure (reduced view, position and mobility of the vocal cords) and the level or levels of airway compromise.

Treatment

The interventions available depend on the environment that the patient is in as well as the skill set and experience of the clinician (**Box 72.2**). It is important to remember that there can be rapid changes in the condition of the patient and that frequent revaluation is needed to respond appropriately to new symptoms and signs. Temporizing interventions should be utilized where possible initially; although tracheostomy is the definitive management

BOX 72.2 Principles of intervention in upper airway obstruction

- Secure the airway with the most straightforward and least invasive method.
- Adequate airway control must include securing the airway below the lowest level of obstruction.
- If known, coexisting medical conditions should be considered when deciding on the most appropriate intervention.
- Only address other medical problems once the airway has been adequately secured.

for upper airway obstruction, it may be difficult due to patient agitation (including effects of hypoxia) and movement (with use of accessory muscles of respiration).

The methods available for patient support in upper airway obstruction can be considered under the broad headings of non-invasive medical management and the use of alternative airways.

Medical management and non-invasive procedures

Whilst it should be borne in mind that 'the time to do a tracheostomy is when you first think of it', there are frequently times when minor trauma, infection or tumours cause airway obstruction that is moderate in severity and stable. Under such circumstances, it may be reasonable to institute a period of close observation allowing supportive and therapeutic measures to be commenced. This option is only suitable for clinicians who have experience in the management of patients with airway obstruction, and facilities exist for immediate intervention by intubation or tracheostomy in the event of patient deterioration. The most appropriate environment for such observation is in a high dependency setting, such as an intensive care unit. During this period, the airway should still be considered as potentially unstable and so all those involved in the management of such a patient must understand that any deterioration is an indication for immediate intervention to secure the airway.

INTERVENTIONS FOR OBSTRUCTION SECONDARY TO FOREIGN BODIES

In the case of upper airway obstruction due to a foreign body, including a food bolus, a stepwise approach is followed. Initially the patient is encouraged to cough. If this fails, then hard blows to the back with the heel of the hand is advocated before considering potentially more hazardous interventions including abdominal thrusts (the Heimlich manoeuvre). This manoeuvre involves the rescuer hugging the patient from behind and exerting pressure with the hands in the region of the xiphisternum to produce diaphragmatic movement. The lungs are compressed which may lead to dislodgement of the impacted foreign body. Complications of this technique include pneumomediastinum, pneumopericardium, surgical emphysema and gastric rupture. If the patient becomes unconscious, the emphasis switches to performing cardiopulmonary resuscitation. Inspection with a laryngoscope and removal under direct vision may be required. Where there is inability to remove the object a cricothyroidotomy is required.

OXYGEN AND HELIOX

The inspiratory oxygen concentration can be increased with the administration of high-flow oxygen via a facemask with a reservoir bag. In the emergency situation, the use of oxygen can be combined with simple airway methods including chin lift and jaw thrust. Use of humidification helps to break down secretions and makes them easier to clear. Heliox is a mixture of 80% helium with 20% oxygen. The properties of helium are a gas with low density and high viscosity resulting in less turbulence compared with air and pure oxygen. The patient experiences reduced resistance during breathing heliox and this is of proven benefit in the obstructed patient.[1]

STEROIDS

Steroids have a role to play in reducing the oedema produced by trauma, inflammation or infection.[2] There is no evidence to suggest a detrimental effect of steroids in the presence of infection when used as a short-term measure. Further indirect evidence on the benefit of steroids is provided by the use of corticosteroids to reduce the risk of post-extubation upper airway obstruction in adults and children.[3, 4]

ANTIBIOTICS

Antibiotics should be given in any case where acute infection is suspected and in cases where there is evidence or strong suspicion of a mucosal injury. Choice of antibiotic is usually guided by local institutional antimicrobial policy.

Alternative airways

The decision to proceed with the use of an alternative airway is based on an unstable patient and includes deteriorating obstructive symptoms and signs despite simple interventions. Patients in this situation are very challenging and appropriately trained and experienced individuals should carry out these interventions.

ORAL AIRWAY

In the event of a loss of consciousness or obstruction due to nasal injury, the airway may be improved with the use of an oral Guedel airway (**Figure 72.1**). A Guedel airway will not be tolerated if the gag reflex is present. This oral

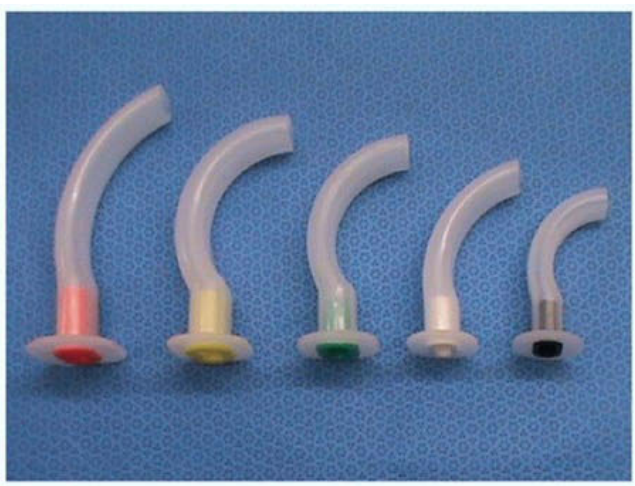

Figure 72.1 Selection of Guedel airways.

airway is easy to insert and bypasses obstruction in the oral cavity and nose but it is easily displaced. It can be used to assist ventilatory resuscitation with a facemask and ambubag. It also facilitates suctioning of the airway. The patient must still have a normal airway beyond the oral cavity and nasopharynx as well as a normal ventilatory drive for this intervention to be of value.

NASOPHARYNGEAL AIRWAY

A nasopharyngeal airway is a soft silicone plastic tube designed to be inserted via the nasal passageway to bypass obstruction at the level of the oropharynx, for example where the tongue base is pushed backwards in Ludwig's angina or angioedema and in cases of trauma with facial fractures (**Figure 72.2**). Insertion is straightforward and the tubes are well tolerated. The nasopharyngeal airway also facilitates suction. It should be noted that the tube can cause trauma to the nasal airway and resulting bleeding may give rise to further airway compromise. Use is contraindicated in patients with severe head or facial injuries where a skull base fracture allows the possibility of entering the intracranial compartment.

ENDOTRACHEAL INTUBATION

Endotracheal intubation is the intervention of choice where there has been a loss of respiratory drive necessitating assisted ventilation, or in cases of progressive upper airway obstruction. The person performing intubation should be supported by a trained assistant with access to a trolley containing a variety of laryngoscopes with a good light source, a range of endotracheal tubes, bougies and suction facilities.[5]

The usual route of intubation is via the mouth. This can be assisted by video-laryngoscopic devices.[6] The relative contraindications include cervical spine fractures, severe facial trauma and laryngeal trauma. In cases of cervical spine fracture, great care must be taken to avoid neck extension that may precipitate or worsen spinal cord injury. Facial trauma is usually associated with increased difficulty visualizing the larynx due to oedema, mucosal laceration and bleeding, trismus and bony instability. Great care is needed where there is laryngeal trauma, as the act of intubation may worsen the existing damage.

An alternative route to secure the difficult airway is by transnasal intubation. This is often performed using endoscopic guidance. The endotracheal tube is secured to a flexible nasal endoscope or bronchoscope (**Figure 72.3**). The tip of the endoscopic device is passed via the larynx into the trachea and the endotracheal tube is then passed over the fibre-optic endoscope into position. This is a skilled technique that requires experience, given the expected airway compromise with secretions, blood, and anatomical distortion resulting in poor views of the larynx.

TRANS-TRACHEAL CANNULATION

In the emergency setting, the trachea can be cannulated directly via the cricothyroid membrane using a large bore intravenous cannula. The airway can then be maintained temporarily by connecting the cannula to an ambubag using a syringe with a 7mm endotracheal tube adaptor inserted in the barrel (**Figure 72.4**).

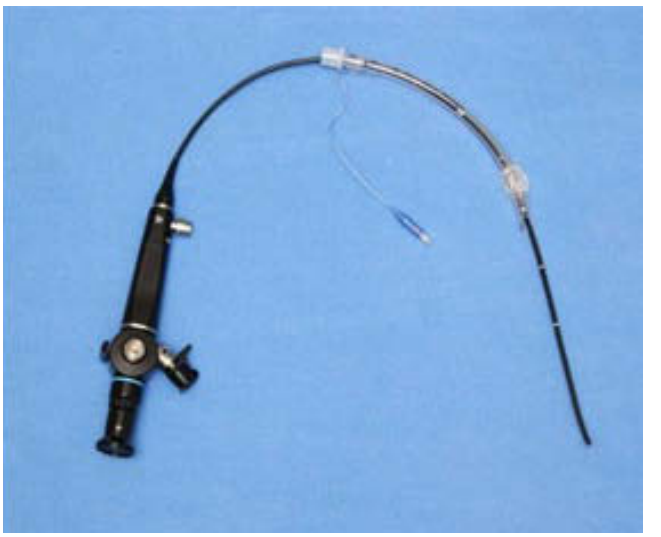

Figure 72.3 Flexible nasal bronchoscope with endotracheal tube.

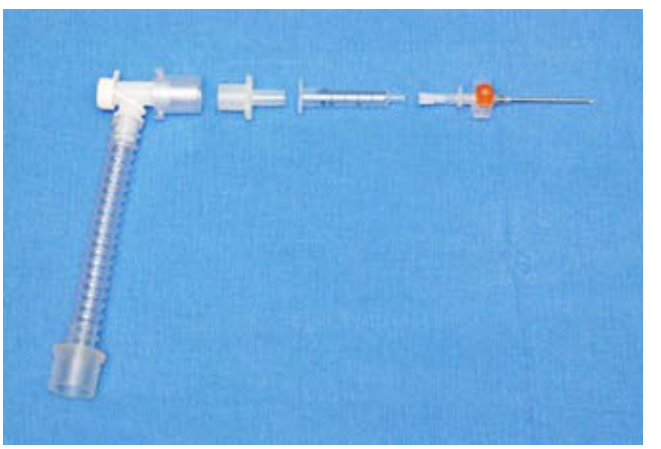

Figure 72.4 Large bore cannula with adaptation to connect to anaesthetic circuit.

Figure 72.2 Nasopharyngeal airway.

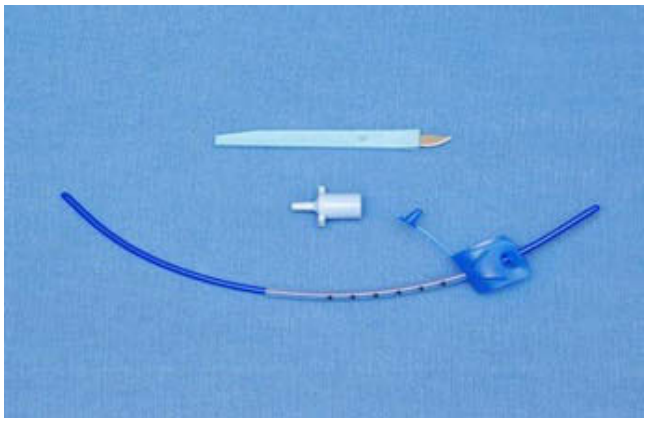

Figure 72.5 Cricothyroidotomy kit.

CRICOTHYROIDOTOMY/MINITRACHEOSTOMY

In an emergency, rapid control of the upper airway can be achieved by use of an airway inserted through the cricothyroid membrane. Once an incision has been made through the membrane a minitracheostomy tube or a wide bore cannula can be used to keep the tract open and provide an alternative airway (**Figure 72.5**). A sound knowledge of the anatomy and technique is required to minimize complications.[7]

The patient is positioned with the neck extended over a pillow. The cricothyroid membrane can be palpated and the area is infiltrated with local anaesthetic and epinephrine. The cricothyroid membrane can be incised either with a scalpel or a wide bore cannula attached to a syringe half filled with saline. In the former case, once the airway has been opened the blunt handle of the scalpel can be inserted and rotated to create space for a tube to pass into the trachea. In the latter case, the needle of the cannula is used to breach the membrane and as the needle and cannula are inserted the plunger of the syringe is withdrawn. Air bubbles into the syringe when the trachea has been entered. The cannula can then be introduced over the needle. The cannula can be connected via a universal connector to an ambubag and the patient can be ventilated for a short period of time. Using this system, CO_2 is not cleared and so conversion to a formal tracheostomy should be undertaken as soon as possible.

A minitracheostomy tube should not be left in situ for more than a short time as there will inevitably be some friction between it and the cricoid cartilage that will predispose the patient to subglottic stenosis.

TRACHEOSTOMY

Tracheostomy (**Box 72.3**) is one of the oldest surgical procedures.[8] There are references to the creation of a surgical airway in many ancient texts.[9] Until the end of the 19th century and the introduction of asepsis together with the development of safe anaesthetic techniques, the procedure was extremely hazardous. Tracheostomy was seen as a last resort in hopeless cases and was the cause of great anxiety for the patient and surgeon alike. Chevalier Jackson established the principles of the operation at the beginning of the twentieth century and these remain in place today.[10] The development of percutaneous tracheostomy has taken surgical airway management out of the exclusive province of the otolaryngologist. There is now a wide variety of clinicians involved in the challenges of tracheostomy care and decannulation strategies.

BOX 72.3 Definitions

Tracheotomy: a surgical opening in the trachea
Tracheostomy: the creation of a stoma at the skin surface that leads into the tracheal lumen

The commonest use of an elective temporary tracheostomy is for prolonged ventilatory support in a ventilated patient. A temporary tracheostomy may also be planned as part of a major surgical procedure in which there are concerns about post-operative swelling or bleeding, which may precipitate upper airway obstruction.

An emergency tracheostomy is a rare procedure, perhaps only indicated in cases of severe trauma or very late presentation. In all other cases, it could be argued that the performance of an emergency tracheostomy is indicative of an underestimation of the severity of the breathing problem. The majority of cases can be dealt with by carrying out an urgent procedure under local anaesthesia with the patient awake. In extremis, it should be possible to perform a cricothyroidotomy and maintain ventilation via a wide bore cannula until conversion to a formal tracheostomy can be undertaken.

A permanent or 'end' tracheostomy is an elective procedure carried out as part of a surgical procedure involving the removal of the larynx, such as a laryngectomy or pharyngolaryngectomy. A permanent tracheostomy is also created in laryngeal diversion procedures used to prevent aspiration. The continuity between the laryngopharynx and the trachea is permanently disrupted and the cut end of the trachea is sutured to the skin.

The effects of tracheostomy are shown in **Box 72.4**.

Indications for tracheostomy

Indications for tracheostomy are: upper airway obstruction; prolonged ventilation; removal of secretions; and part of another procedure.

UPPER AIRWAY OBSTRUCTION

This has been discussed above. Tracheostomy is considered as the ultimate form of airway control.

BOX 72.4 Effects of tracheostomy

- Laryngeal bypass – loss of cough and phonation
- Reduction in respiratory dead space
- Loss of nasal mucosa filtration and humidification
- Increased risk of infection
- Tube acts as foreign body leading to local inflammation
- Sump above tracheostome and below larynx where mucus collects.

PROLONGED VENTILATION

Tracheostomy is the safest means of assisting ventilation where prolonged positive pressure is needed. It is easier to secure a tracheostomy tube than either an orotracheal or nasotracheal tube and the reduced dead space assists weaning of respiratory support. It has been demonstrated that the introduction of percutaneous tracheostomy has led to a doubling in the number of tracheostomies being carried out.[11] It may be that the ease of access to tracheostomy has resulted in reduced duration of intubation.[11] However, with the introduction of low-pressure cuffs for endotracheal tubes, a longer period of intubation has become acceptable. There is evidence that early tracheostomy in trauma patients reduces length of ventilation and hospital stay[12] and it may be that the same applies for general ITU patients.

REMOVAL OF SECRETIONS

The accumulation of secretions in the lower respiratory tract is responsible for a reduction in gas diffusion within the alveoli. This results in respiratory failure. A tracheostomy reduces the dead space, so reducing the work of breathing, and also makes it easier to aspirate secretions with less patient discomfort.

PART OF ANOTHER PROCEDURE

A permanent tracheostomy is an unavoidable consequence of a major head and neck procedure (e.g a total laryngectomy). A temporary tracheostomy is usually needed for open resections involving the oropharynx or larynx. In these cases, the tracheostomy allows protection of the lower airway from aspiration of blood in the event of a haemorrhage, as well as guarding against upper airway obstruction from post-operative swelling. A percutaneous tracheostomy is probably not appropriate in these cases, as the pre-tracheal tissues fit tightly around the tube.[13] In the event of tube displacement, the tissues can collapse inwards, closing the airway with a potentially fatal outcome.[14]

Anatomy

As with any surgical procedure, when performing tracheostomy, it is essential to have a sound knowledge of the relevant applied anatomy of the upper trachea. Problems are likely to happen if the surgeon strays from the midline. The recurrent laryngeal nerve runs in the tracheoesophageal groove and the great vessels are lateral to this within the carotid sheath. It is rare in a straightforward tracheostomy to lose sense of where the midline is, but in obese patients and small children it is possible to lose the anatomical landmarks and stray laterally. The thyroid isthmus crosses in front of the trachea covering a variable number of the tracheal cartilaginous rings. It is a highly vascular structure and inadvertent damage during dissection or friction from the tube may result in post-operative haemorrhage. The innominate artery crosses the front of the trachea, from left to right, at a variable height. In cases of a high innominate artery it may be encountered during dissection or may suffer erosion from the tracheostomy tube with potentially fatal post-operative haemorrhage.[15]

Contraindications

There are no absolute contraindications to tracheostomy. However, in patients with a terminal prognosis, very careful consideration must be given to the psychological effect on the patient and the quality of life aspects. There is no right or wrong answer and each patient must be approached on an individual basis.

Pre-operative considerations

In the elective setting it is imperative that adequate consent is received from the patient or their relatives. As part of this process it is necessary to cover the risks and benefits of the procedure in some detail. This must be a frank and open discussion and the potential complications and sequelae of tracheostomy must be pointed out. This is particularly true of paediatric tracheostomy.

Operative procedures

PERCUTANEOUS TRACHEOSTOMY

First described more than 50 years ago,[16] this technique has grown in popularity and is now the commonest procedure for the provision of an alternative airway for ITU patients. The growth of the procedure followed the introduction over the last 15–20 years of commercial kits based on well defined techniques (**Figure 72.6**).[17–19] The most commonly employed kit in the UK depends on the dilatation technique originally described by Ciaglia.[20]

The patient should be positioned as for a formal surgical tracheostomy (see 'Open surgical tracheostomy' below). The trachea is punctured, using a needle and cannula, just below the first tracheal cartilage ring. A syringe half-filled with saline is attached to the cannula. Gentle aspiration allows correct positioning of the cannula,

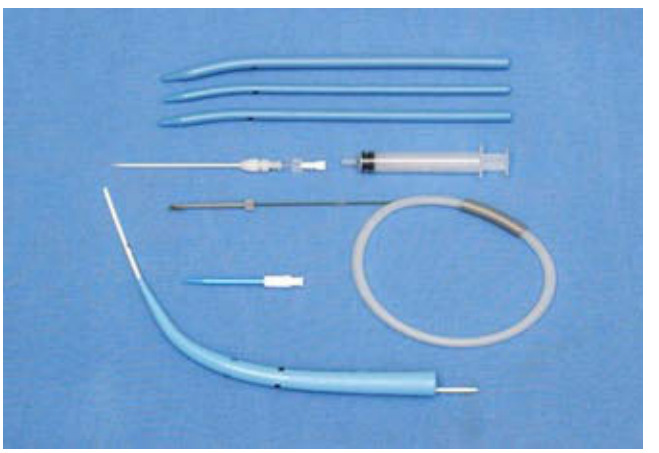

Figure 72.6 Percutaneous tracheostomy set.

because air is aspirated through the saline as the needle passes into the trachea. The needle is withdrawn and a guide wire is inserted through the cannula. The cannula is withdrawn to allow for either a single dilator or a series of dilators with increasing diameter to be passed over the guide wire. The dilators create a passage that is wide enough for the insertion of a standard tracheostomy tube, which is secured in position within the trachea. It is advisable to view the internal lumen of the trachea during this procedure by using a flexible bronchoscope, as this may reduce complications.[19]

OPEN SURGICAL TRACHEOSTOMY

There are many variations in the technique of open surgical tracheostomy but they are all based on the same fundamentals. The technique described is that preferred by the authors. The procedure should, when possible, be carried out in an operating theatre, under sterile conditions. It is usual for the patient to have a general anaesthetic but where this is deemed hazardous the procedure can be carried out under local anaesthetic.

The patient should be positioned supine, with the neck extended by placing a sandbag under the shoulders. It is important that the patient is positioned square on the table with the shoulders at the same level as this will ensure that the midline structures of the neck are truly in the midline throughout the operation (**Figure 72.7a**). When operating under local anaesthesia it may be necessary to compromise on the degree of neck extension as over-extension may further restrict the airway.

A horizontal incision is sited halfway between the sternal notch and the lower border of the cricoid cartilage (**Figure 72.7b**). Once the skin has been incised, dissection continues through the subcutaneous tissues to the strap muscles, which are retracted laterally, following blunt dissection in the midline to separate them. Following this manoeuvre, the thyroid isthmus should be visible (**Figure 72.7c**). The isthmus should be clamped, divided and transfixed (**Figure 72.7d**). At this point the anterior tracheal wall is encountered. It is useful to identify the cricoid cartilage to plan the point of entry into the trachea. Ideally the tracheotomy should be made between the 2nd and 4th tracheal rings. Before entering the trachea, it is important to select an appropriately sized tracheostomy tube and check that the cuff and all connecting equipment works properly, so that ventilation can continue uninterrupted following the tracheostomy. There needs to be good communication between the surgeon and the anaesthetist.

Having informed the anaesthetist that the trachea is about to be opened, the tracheotomy can be performed. The guiding principle should be to cause as little disruption to the trachea as possible, maintain cartilage and prevent damage to the cricoid cartilage. These aims are best achieved by the use of a vertical slit between stay sutures. Once the trachea has been opened, the anaesthetist should withdraw the endotracheal tube under the direction of the surgeon, who can visualize the tube being withdrawn. When the tip of the endotracheal tube is immediately above the tracheotomy, withdrawal can stop and the tracheostomy tube should be inserted. The cuff should be inflated and the tube connected to the ventilator.

The incision should be closed loosely and the tracheostomy tube secured in position with tapes, sutures or both (**Figure 72.7e**).

Choice of tube

There is a wide variety of tracheostomy tubes available, made from different materials and with different features. The choice of tube depends on the indication for the tracheostomy, the post-operative needs of the patient and the anatomy of the patient.

CUFF

Cuffed tracheostomy tubes are used to provide a seal to allow positive pressure ventilation or to prevent aspiration. The pressure of air within the cuff must be high enough to provide an adequate seal but not so high as to damage the tracheal mucosa resulting in subglottic stenosis. The use of modern low-pressure cuffs has for the most part reduced this problem.

INNER TUBE

Some tubes are supplied with an inner tube that fits snugly inside the main tube. The tip of the inner tube projects a few millimetres beyond the distal end of the main tube. This means that secretions will collect in the inner tube that can be removed, cleaned and replaced without disruption to the patient or their airway.

FENESTRATION

The fenestration is sited at the point of maximum curvature in the tube and may be in the form of a single hole or a number of small holes. The fenestration allows air to pass from the tube through the larynx, so increasing the air available for phonation and increasing the volume of the voice.

FLEXIBILITY

In some cases, a rigid tracheostomy tube will not conform to the anatomy of the patient and will lie at an awkward angle or in a position that will result in tracheal trauma from the tip of the tube rubbing against the tracheal wall. In these circumstances, a softer and more flexible tube is preferred. If the use of a softer tube results in obstruction of the tube due to kinking, it may be necessary to use an armoured flexible tube.

ADJUSTABLE FLANGE

An adjustable flange allows the intra-tracheal length of the tube to be altered to take account of the depth of the stoma, which may be increased by alterations in anatomy, such as in patients with a large thyroid mass, or to bypass intra-tracheal obstruction.

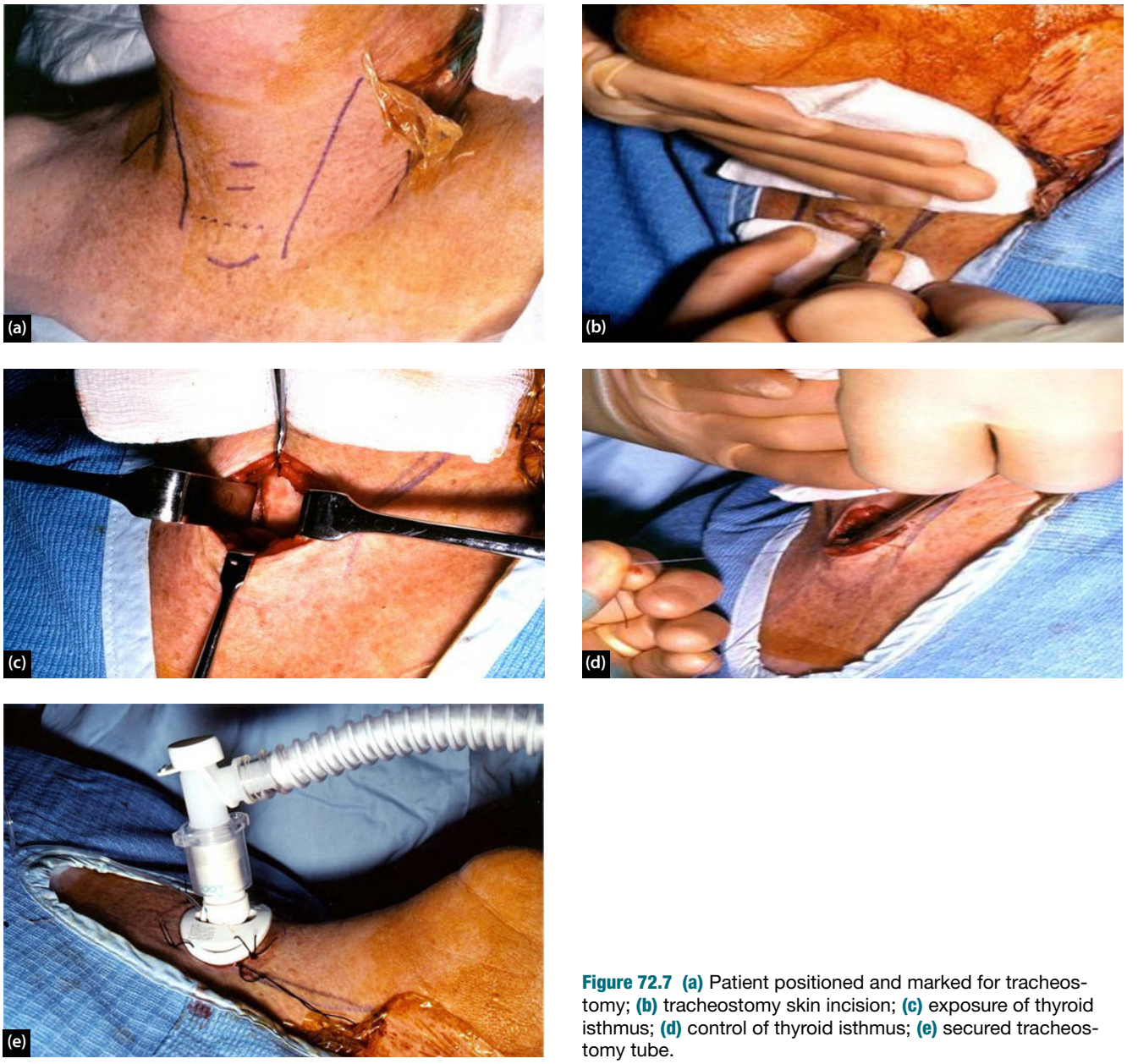

Figure 72.7 **(a)** Patient positioned and marked for tracheostomy; **(b)** tracheostomy skin incision; **(c)** exposure of thyroid isthmus; **(d)** control of thyroid isthmus; **(e)** secured tracheostomy tube.

The tube placed at the time of the tracheostomy should be cuffed to allow ventilation of the patient and to prevent aspiration of blood or secretions resulting from the procedure. Ideally an inner tube should be available to allow easy clearing of secretions in the immediate post-operative period.

Post-operative considerations

It is important to remember that the patient requires multidisciplinary input. In addition to the requirements arising from the tracheostomy, which include communication, airway management and potential swallowing issues, there is also the need to address the pathological process that has generated the need for definitive airway control. A team-based approach is therefore essential for optimal patient outcome and minimizing complications with various studies and consensus.[21–24]

On return to the ward it is important that a nurse who is experienced in the care of tracheostomy patients and knowledgeable about the potential complications looks after the patient. Writing materials must be available for the patient to use for communication.

The original tracheostomy tube must be secured in position for at least 3 days to allow a good tract to form. The tube should be changed after 7 days and any sutures can then be removed. Tubes should be secured with tapes fastened by a secure knot on both sides of the neck, with the neck in a neutral position. If the neck is extended when the tapes are fastened, then the tapes will be too long and will not hold the tube in the appropriate position and it may be coughed out.

The cuff should be deflated once the risk of aspiration has passed. In most cases, there is no need for cuff inflation after the first 12 hours.

Following tracheostomy, the inspired air passes directly into the trachea without being warmed and humidified by the upper airway. As a result, the air is irritant to the trachea and there is an increase in the quantity and viscosity of the tracheal secretions. The patient may require frequent suctioning in the early post-operative period and the use of hot water bath humidifiers or nebulizers is essential to reduce the risk of tube obstruction due to crust formation. As the trachea becomes accustomed to the presence of the tube and the patient learns to clear the secretions by coughing through the tube, so the need for suctioning and humidification decreases.

Swallowing problems are common following tracheostomy. These are usually due to the sensation of pressure in the upper oesophagus because of an inflated cuff and because the movement of the larynx during swallowing is reduced secondary to the tethering effect of the tube.

If at any stage doubts occur regarding the position of the tube or obstruction of the lumen, a flexible nasal endoscope can usually be passed through the tube to inspect the lumen of the tube and the trachea.

Complications

Complications can be:

- Immediate (haemorrhage; air embolism; local damage)
- Intermediate (extubation; obstruction; subcutaneous emphysema; infection; fistulae)
- Late (tracheo-cutaneous fistula; tracheal stenosis).

IMMEDIATE

Haemorrhage is the commonest fatal complication of tracheostomy,[25] as well as the commonest complication. Bleeding is usually due to damage to the thyroid veins or the thyroid isthmus. If there is significant bleeding at the end of the procedure the wound should be explored and any bleeding vessel ligated. Packing the tracheostomy wound to tamponade the bleeding is widely practised but should be seen as little more than a temporary procedure prior to re-exploration of the wound.

Air embolism, while life threatening, is fortunately rare following tracheostomy. If the large veins of the neck are opened during the procedure air may be sucked into the venous system and pass into the right atrium.

Damage to structures in the vicinity of the operative field is often the result of altered anatomy or inattention to good surgical technique. Inexperienced surgeons may inadvertently stray from the midline and so cause damage to the contents of the carotid sheath, oesophagus or recurrent laryngeal nerve. In emphysematous patients, the apex of the lung may extend into the lower neck and can be damaged because of lateral dissection. An inadequate incision, poor retraction or poor haemostasis can result in less than ideal exposure and consequent damage to the tracheal walls or cricoid cartilage. Damage to the cricoid is particularly serious and if recognized at the time of surgery, the tracheostomy should be re-sited lower in the trachea and the damage repaired.

Immediate complications are best prevented by good haemostasis during surgery and meticulous attention to surgical technique.

INTERMEDIATE

Accidental extubation is easily avoided provided that the tube is adequately secured at the time of the procedure, by suturing the flanges of the tube to the skin. If the tube is displaced and comes to lie in the pre-tracheal space, the complication may not become immediately apparent. The patient continues to breathe as the soft tissues gradually prolapse around the tracheal opening, which slowly begins to seal. Dyspnoea slowly increases and by the time the displacement is apparent the tube may be impossible to replace as the tracheotomy has virtually closed. An experienced nurse will pick up on the early warning signs. Any difficulty breathing through the tube must be fully investigated. The use of a flexible scope passed through the lumen of the tube may identify displacement or obstruction of the tube due to crusting, granulation tissue or poor placement of the tube tip with respect to the tracheal wall.

If the tracheostomy tube or the trachea are obstructed and the skin incision has been closed tightly, then air may be forced out into the soft tissues of the neck during expiration resulting in subcutaneous emphysema. Surgical emphysema, under these circumstances, can track up to the lower eyelids and down into the upper chest. In severe cases the swelling may cause displacement of the tube.

Tracheo-oesophageal fistulae may be the result of intra-operative damage to the posterior wall of the trachea or persistent rubbing of the tip of the tube on the posterior wall in the early post-operative period. The fistula usually presents when the patient starts to show signs of aspiration despite the cuff being inflated. Tracheo-arterial fistulae present most commonly in previously irradiated patients, particularly if a low tracheostomy has been carried out. There is rarely any premonitory sign and the usual presentation is with sudden massive haemorrhage. The tracheostomy tube must be changed immediately for a cuffed tube; the cuff should be inflated to prevent further aspiration of blood and compression applied to any bleeding vessel via the tracheostome. The wound should be explored immediately as there is a very high mortality associated with this complication. The commonest artery affected is the innominate although there are reports of trachea-carotid fistulae.[26]

LATE

Epithelialization of the tract is a normal event in the evolution of a tracheostomy. The longer the tracheostomy has been present the more established the process is and the more likely the tract is to persist following decannulation. The incidence can be reduced if great attention is paid to ensuring an airtight seal is maintained once the stoma has been occluded. If there is evidence of granulation tissue

in the fistula, simple cautery with silver nitrate may assist spontaneous closure. A small number of cases will require formal surgical closure. This involves excision of the tract all the way down to the anterior tracheal wall and closure in several layers.

Tracheal stenosis is almost always the result of damage to the cricoid or first tracheal ring at the time of surgery or damage to the trachea from the rubbing of a poorly positioned tube, resulting in mucosal inflammation.

Decannulation

If the patient is able to breathe around the tube when it is occluded then there is no need to downsize the tube, which is usually the case if the initial cuffed tube has been replaced with an uncuffed fenestrated tube. Decannulation should take place in an ordered sequence. The tube should be blocked during the day and unblocked at night for the first 24 hours. If the patient tolerates this then the tube can be occluded for a full 24-hour period and if this is tolerated then the tube can then be removed. If the patient is unable to tolerate this occlusion of the tube then it may be necessary to downsize the tube to give more room around it. Patients who have been dependent on the tracheostomy for a long time may require a more prolonged decannulation process as it may take some time for them to overcome their anxiety about being unable to breathe without the tube in place. Variability in practice regarding the exact timing of tracheostomy still occurs.[27]

Once the tube has been removed an airtight dressing must be applied to occlude the stoma. In most cases, several gauze squares covered with an occlusive dressing will be sufficient. The dressing should be changed whenever an air leak appears to improve the chance of full closure of the fistula.

The national tracheostomy safety project

The National Tracheostomy Safety Project aims to produce a national tracheostomy safety resource and, through its membership of the Global Tracheostomy Collaborative, is working to improve the care of tracheostomy patients in all countries. Its website (www.tracheostomy.org.uk) provides a variety of open access educational resources and protocols for the management of patients.

TRACHEOSTOMY-SPARING INTERVENTIONS

Advanced cancers of the upper aerodigestive tract may present with significant upper airway obstruction. Many of these patients are managed with an awake tracheostomy under local anaesthetic or, following successful intubation, have a tracheostomy to secure their airway prior to anaesthetic reversal.

In certain situations of locally advanced upper aerodigestive tract carcinoma, other interventions may be used to re-establish a satisfactory airway and avoid the need for a surgical tracheostomy. Debulking of the tumour can be achieved, for example, with the use of a carbon dioxide laser (**Figures 72.8** and **72.9**), a microdebrider or biopsy forceps. Tumour debulking is a relatively low risk procedure, without the risks and morbidity associated with tracheostomy. It is especially suited for supraglottic tumours, but less effective for subglottic neoplasms. At the same time as achieving an improved airway, the debulking allows for samples to be harvested for histologic analysis. The operating surgeon can also gain a better appreciation of the clinical extent of the tumour. The avoidance of tracheostomy placement has several advantages: the potential for 'seeding' of the carcinoma to the stoma site is abrogated; incision planning is less complex if a laryngectomy is required for definitive treatment; and hospital stay is reduced.

These interventions are highly complex undertakings and significant combined expertise on the part of the anaesthetic and surgical teams is required to ensure a good outcome.[28] Good communication between the teams, including a thorough pre-operative briefing of all staff involved of what is expected as well as alternative

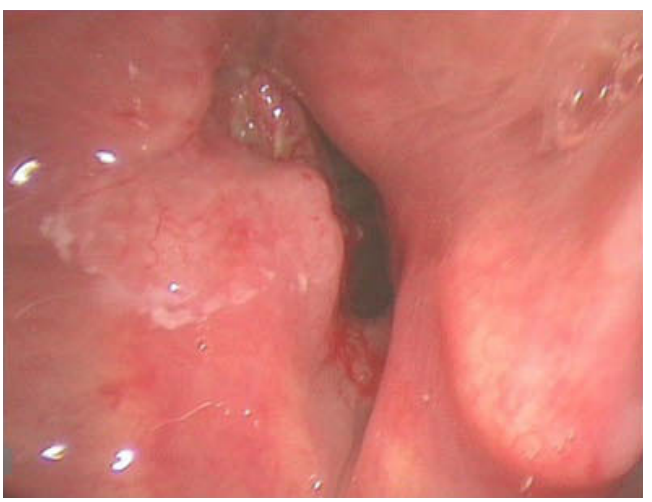

Figure 72.8 Left-sided laryngeal carcinoma involving supraglottic and glottic regions.

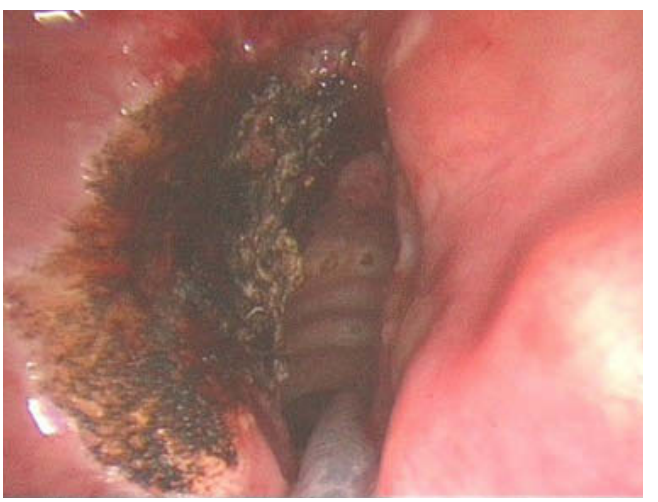

Figure 72.9 Airway following laser debulking.

strategies in the event of problems encountered, forms part of the expertise needed.

The presence of a tracheostomy tube can make radiation planning difficult and, where feasible, debulking can be repeated to achieve a stable airway.[28] There is evidence of a significant delay in starting definitive treatment for patients who undergo tracheostomy when compared with those undergoing debulking procedures.[29]

EMERGENCY AIRWAY MANAGEMENT DURING A 'CAN'T INTUBATE, CAN'T OXYGENATE' (CICO)

There has been a debate in recent years as to the safest way to secure the airway in the event of an emergency event in which it is not possible to intubate or oxygenate a patient (can't intubate, can't oxygenate, or CICO). The traditional approach by ENT surgeons has been to perform an emergency or 'crash' tracheostomy. However, over the last 10–20 years there has been a decrease in the number of routine open tracheostomies carried out as more percutaneous tracheostomies are performed in the intensive care setting. The National Confidential Enquiry into Patient Outcome and Death (NCEPOD) tracheostomy report, '*On the right trach?*' reviewed the care received by patients who underwent a tracheostomy.[30] This review reported that the majority of open tracheostomies are performed as part of another surgical procedure (major head and neck resection) or in patients who might be considered 'unfavourable' for a percutaneous procedure. The follow-on from this is that there are fewer opportunities for trainees to acquire skills to perform an open tracheostomy.

So, when called to an airway emergency, what is the most appropriate, safest and quickest technique to use to secure the airway? Ultimately the decision rests with the individual and must be based on their experience and ability as well as an assessment of the patient, the skills of other team members and the available equipment. However, a good argument can be made that the quickest and safest way to secure the airway is by the use of the 'Scalpel–Bougie' technique of cricothyroidotomy. This technique has been supported by the Difficult Airway Society in the UK for front of neck airway (FONA) in CICO events.[31] The technique is different from the standard 'needle' cricothyroidotomy, which has been shown to be ineffective in altering the outcome in CICO events.[32] A recent editorial with a multidisciplinary authorship has advocated that there should be an emphasis on Scalpel-Bougie cricothyroidotomy training for all medical professionals involved in the management of acute airway emergencies.[33]

KEY POINTS

- Assessment of the airway should be part of an overall systematic approach to managing the critically ill patient.
- The assessment should determine the level(s) of airway obstruction.
- Action should be decisive.
- The least invasive intervention that will bypass the level of the lowest obstruction should be used.
- Problems from comorbidities should be considered, particularly in cases of multiple trauma.
- Any intervention should be carried out by someone who is experienced in the use of that technique.
- The technique chosen to effect tracheostomy should minimize trauma whilst achieving the desired outcome of a secure airway.

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CHAPTER 73

PHYSIOLOGY OF SLEEP AND SLEEP DISORDERS

John O'Reilly

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Central disorders of Hypersomnolence 1055
Circadian rhythm SLEEP-WAKE disorders 1056
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SEARCH STRATEGY

Data in this chapter may be updated by a PubMed search using the keywords: sleep disorders, classification of sleep disorders, sleep physiology, sleep deprivation, excessive daytime sleepiness, hypersomnia, insomnia, sleep-related breathing disorders, obstructive sleep apnoea, central sleep apnoea, sleep hypoventilation, obesity, hypoventilation, central disorders of hypersomnolence, narcolepsy, cataplexy, circadian rhythm sleep-wake disorders, parasomnias, sleep-walking, REM behaviour disorder, sleep-related movement disorders, restless legs syndrome, periodic limb movement and bruxism.

INTRODUCTION

Sleep is essential as a restorative process to maintain cognitive performance and work productivity as well as physical, psychological and emotional well-being. Although muscles may not need sleep, the brain needs sleep to function and control movements and thoughts.[1]

Normal sleep physiology

Sleep physiology may be assessed by polysomnography (PSG), which typically comprises sleep staging using electroencephalography (EEG) with multi-channel recording of video, snoring, nasal airflow, and thoracic and abdominal respiratory effort to produce an apnoea-hypopnoea index (AHI), as well as sensors to detect body position and leg movement. EEG and video are often omitted in assessment of subjects who are likely to have sleep-related breathing disorders, facilitating portable (ambulatory) or home monitoring as cardio-respiratory polygraphy (**Figure 73.1**).

During normal sleep, polysomnography (PSG) shows that subjects cycle through periods of light sleep (stages 1 and 2), deep sleep (N3 comprising former stages 3+4) in which the brain is resting and becomes refreshed, and rapid eye movement (REM) sleep in which the brain is active in consolidating thoughts, learning and memory (**Figure 73.2**).

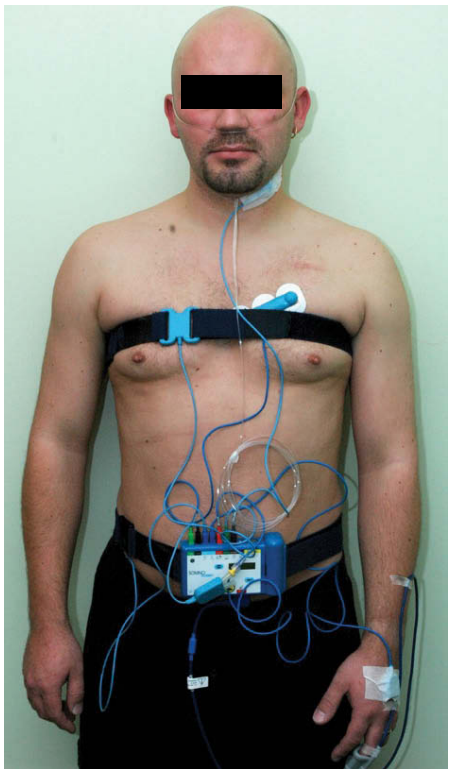

Figure 73.1 Cardio-respiratory polygraphy study (portable monitoring).

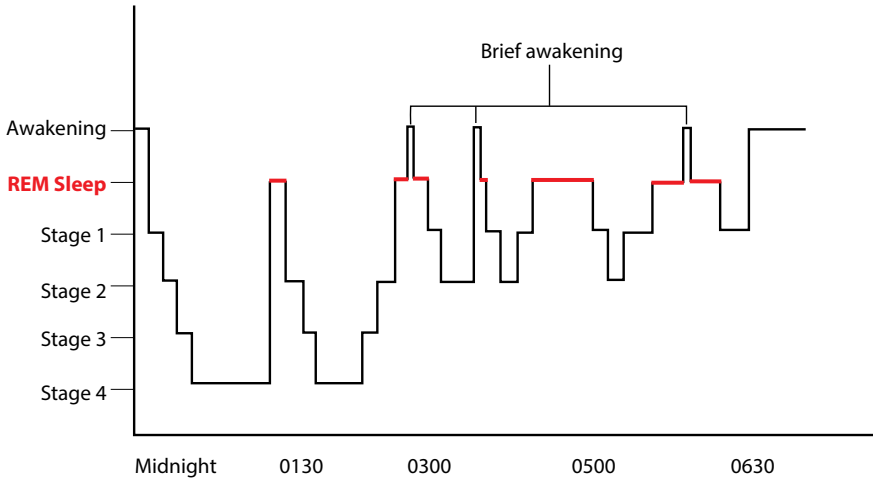

Figure 73.2 Sleep staging using polysomnography.

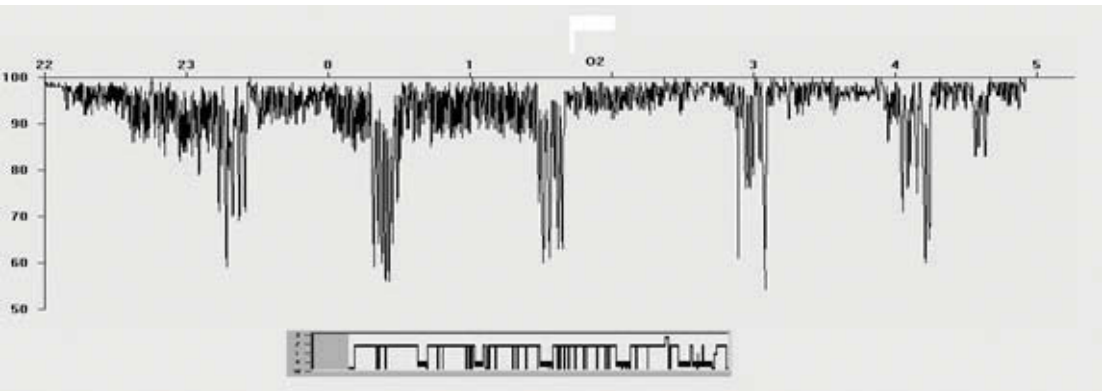

Figure 73.3 REM-related increase in frequency of nocturnal oxygen desaturation due to ventilatory failure in obstructive sleep apnoea.

As the night progresses, periods of deep sleep become shorter, while REM periods become longer. In REM sleep, pathognomonic rolling eye movements are noted, and there is generalized inhibition of skeletal muscles, including the intercostal, accessory and pharyngeal dilators, leaving largely the diaphragm to support ventilation. This is reflected in an increased respiratory rate and ventilatory failure is more likely, particularly in subjects with respiratory or neuromuscular disorders (**Figure 73.3**).

Sleep onset leads to hypoventilation with reduced metabolic rate. There is loss of voluntary and emotional control of breathing, loss of wakefulness drive and a decrease in reticular activating system (RAS) activity rate, leading to dependence on brainstem reflex activity. Reduced ventilation leads to a rise in partial pressure carbon dioxide ($PaCO_2$), and consequent fall in partial pressure oxygen (PaO_2). A small rise in $PaCO_2$ is necessary to exceed the apnoeic threshold and maintain ventilation. There is reduced medullary phasic electrical activity, and reduced chemo-sensitivity to partial pressures of arterial carbon dioxide ($PaCO_2$) and oxygen (PaO_2), together with increased airway resistance.[2, 3] The respiratory system is therefore less able to adapt to changes in sleep, including hypoxaemia.[4]

There is an endogenous circadian rhythm in pulmonary function, respiratory control and basal metabolism, which appears independent of daily changes in behaviour (including sleep) and environment.[5]

During the night there are diurnal falls in cortisol levels and body temperature, and increased cholinergic tone that may lead to increased airflow limitation in patients with chronic obstructive pulmonary disease (COPD).[6]

Sleep deprivation

Acute sleep deprivation leads to impaired cognitive, psychomotor and executive function, as well as increased cortisol, impaired glucose tolerance, androgen deficiency and increased appetite due to a reduced blood leptin/ghrelin ratio.[7–9]

Longer term sleep deprivation may lead to deranged metabolism with obesity, increased insulin resistance and risk of diabetes mellitus, hyperlipidaemia, cardiovascular disease, coronary events and increased all cause mortality.[10, 11]

Sleep deprivation has been shown to have an effect on pulmonary function with significant decline in minute ventilation and inspiratory muscle endurance after 24 hours. This is not clinically significant in healthy subjects, but can lead to a significant 5–6% fall in forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC) in COPD.[12–14]

Sleep restriction and fragmentation may occur due to emotional stress, environmental factors such as shift

work, acute and chronic medical conditions including obesity, and a range of specific sleep disorders.[15–17]

Excessive daytime sleepiness

Excessive sleepiness is a subjective marker of many sleep disorders, although it can affect up to 12% of the normal population, and is more common in subjects with snoring, obesity, diabetes mellitus and renal failure.[18–20]

It is difficult to quantify consistently or objectively, but the Epworth Sleepiness scale (ESS) score is commonly used as a validated simple self-administered assessment tool (**Table 73.1**). A score of more than 10 is considered significant, but lower scores may not exclude sleepiness, possibly due to misinterpretation of the test.[21]

The multiple sleep latency test (MSLT) uses EEG to assess how quickly a subject falls asleep during 5 attempted naps over the course of a day. A shortened mean sleep latency of less than 8 minutes is considered consistent with pathological excessive sleepiness.[22] Sleep diaries (logs) may help to confirm adequate sleep opportunity.

The maintenance of wakefulness test (MWT) conversely assesses how long a subject can remain awake and may indicate reduced alertness if mean sleep latency is less than 20 minutes. Correlation between subjective and objective measurements may be poor.[23]

Psycho-motor vigilance can be measured using the Oxford Sleep Resistance (Osler) test, and in driving simulators.[24, 25]

CLASSIFICATION OF SLEEP DISORDERS

The International Classification of Sleep Disorders describes a range of respiratory and non-respiratory conditions that may be associated with insomnia or excessive daytime sleepiness while awake, or behavioural abnormalities in sleep (**Box 73.1**).

Insomnia

The criteria for insomnia include a report of subjective difficulty with sleep initiation or maintenance, including waking up earlier than desired, resistance to going to bed on appropriate schedule or difficulty sleeping without parent or caregiver intervention. This must be associated with adequate opportunity and circumstances to sleep, and also a requirement for a report of daytime consequences.[22] These include fatigue or malaise, impairment of attention, concentration or memory, impaired social, family, occupational or academic performance, mood disturbance or irritability, daytime sleepiness, behavioural problems (e.g. hyperactivity, impulsivity, aggression), reduced motivation, energy or initiative, proneness for errors or accidents, or concerns about, or dissatisfaction with, sleep.

Many people experience occasional insomnia (50%) with 6–10% describing chronic insomnia.[26] Insomnia is common in a range of medical and psychiatric disorders. Short-term insomnia is often associated with an identifiable cause or trigger, commonly particular daytime stressors.

BOX 73.1 International Classification of Sleep Disorders (ICSD-3)

- Insomnia
- Sleep-related breathing disorders
- Central disorders of hypersomnolence
- Circadian rhythm sleep-wake disorders
- Parasomnias
- Sleep related movement disorders
- Other sleep disorders

TABLE 73.1 Epworth Sleepiness Scale score

How likely are you to doze off or fall asleep in the following situations, in contrast to feeling just tired? This refers to your usual way of life in recent times. Even if you have not done some of these things recently try to work out how they would have affected you.
Use the following scale to choose the most appropriate number for each situation:
0 = no chance of dozing
1 = slight chance of dozing
2 = moderate chance of dozing
3 = high chance of dozing

Situation	Chance of dozing
Sitting and reading	
Watching TV	
Sitting inactive in a public place (e.g a theatre or a meeting)	
As a passenger in a car for an hour without a break	
Lying down to rest in the afternoon when circumstances permit	
Sitting and talking to someone	
Sitting quietly after a lunch without alcohol	
In a car, while stopped for a few minutes in traffic	
TOTAL	

A score of more than 10 indicates significant sleepiness.

Chronic insomnia disorder is defined by symptoms at least three times per week for a duration of 3 months, and is usually only made when the insomnia is especially prominent or unexpectedly prolonged, and under assessment or treatment. It combines a number of categories previously defined as psychophysiological insomnia, idiopathic insomnia, sleep-state misperception and inadequate sleep hygiene.[22]

The diagnosis of insomnia relies on a medical, sleep and psychiatric history and is aided by keeping a sleep log. Predisposing, potentiating and precipitating factors may be identified.

Management of insomnia involves dealing with identified underlying causes, and consideration of behavioural and drug therapies. Sleep hygiene advice includes restriction of caffeine and alcohol, especially during the evening. Cognitive behavioural therapy for insomnia (CBTI) also includes relaxation, stimulus control and sleep restriction techniques.[26, 27]

CBTI is preferred but can be combined with pharmacological treatments including benzodiazepines, non-benzodiazepines and low-dose antidepressants. Hypnotics should be used for a maximum of 2–3 per week to avoid dependence.[28, 29]

SLEEP-RELATED BREATHING DISORDERS

Sleep breathing disorders include a spectrum of problems with similar pathophysiology including obstructive sleep apnoea hypopnoea (OSA), and sleep-related hypoventilation, as well as the less common condition of central sleep apnoea (CSA) (**Box 73.2**). Children and adults with tonsillar hypertrophy, craniofacial syndromes and neuromuscular disorders have an increased risk for sleep breathing disorders.[30]

Although patients may be asymptomatic, ventilatory failure during sleep and consequent sleep fragmentation usually lead to presentation with one or more of a range of associated problems including snoring, subjective sleep disturbance, excessive daytime sleepiness, witnessed pauses in breathing, right heart failure (cor pulmonale) and cardio-metabolic comorbidities. Children may present with insomnia, enuresis, behavioural problems, hyperactivity, and reduced attention span, memory and learning ability. Growth may be impaired due to lack of deep sleep necessary to produce growth hormone.

BOX 73.2 Sleep breathing disorders

Obstructive sleep apnoea (OSA)
Central sleep apnoea (CSA)
- central sleep apnoea with Cheyne-Stokes breathing
- central sleep apnoea due to a medical disorder without Cheyne-Stokes breathing
- central sleep apnoea due to high-altitude periodic breathing
- central sleep apnoea due to a medication or substance
- primary central sleep apnoea
- treatment-emergent central sleep apnoea

Sleep related hypoventilation disorders
- obesity hypoventilation syndrome (OHS)
- sleep-related hypoventilation due to a medical disorder
- sleep-related hypoventilation due to a medical disorder

Sleep-related hypoxaemia disorder

Snoring is generated by the vibration of anatomical structures of the nasopharynx during sleep. Prevalence of habitual snoring ranges from 24% to 50% in men and from 14% to 30% in women and increases with age, obesity, alcohol ingestion and nasal obstruction. Isolated snoring, although asymptomatic, results in social disability and relationship disharmony. General population surveys have found a strong correlation between snoring and daytime sleepiness.[31–33] Snoring with sleepiness as features of obstructive sleep apnoea have been associated with hypertension, ischaemic heart disease, diabetes mellitus and cerebrovascular accident as well as increased morbidity and mortality from road traffic and work related accidents.

Obstructive sleep apnoea (OSA)

OSA is a common condition comprising intermittent complete collapse of the pharyngeal airway, followed by brief arousals or wakenings which then enable return of breathing (**Figure 73.4**). The term obstructive sleep apnoea-hypopnoea (OSAH) is used to include episodes of breathing with reduced amplitude (**Table 73.1**). The condition may be asymptomatic but often presents with witnessed snoring, pauses in breathing or choking during sleep, or with symptoms due to sleep fragmentation including excessive sleepiness, impaired alertness, loss of concentration or memory, comprising the OSAH syndrome (OSAHS).[34–36]

Upper airway resistance syndrome (UARS) is classified as a variant of OSA, characterized by increased airway resistance to breathing during sleep, without cessation of breathing. The primary symptoms are similar to those in OSAS although snoring may not be noted. Sleepiness and excessive fatigue develop due to arousals in sleep with changes in pulse transit time associated with respiratory flow limitation, and increased negative intra-thoracic pressure.[37]

The pathophysiology of OSA includes intermittent hypoxia and possibly sympathetic activation which drive insulin resistance and disordered lipid metabolism.as well as a systemic inflammatory cascade with free-radical production, inflammatory cytokine release and oxidative stress.[38, 39]

Interaction of haemodynamic and inflammatory changes promote vascular endothelial growth factor 3, endothelial dysfunction and vascular remodelling, which may combine to promote the development of atherosclerosis and cardiovascular disease, including heart failure and arrhythmias.[38–41] Organ, tissue or functional impairment is related to the severity of nocturnal hypoxia.[38, 42]

OSA may play a causative role in development of hypertension, insulin resistance and hyperlipidaemia in the cardio-metabolic syndrome, as well as in heart failure, pulmonary hypertension, coronary artery disease, arrhythmias and cerebro-vascular accidents.[36, 42–50]

Patients with heart failure may have less subjective daytime sleepiness despite significantly reduced sleep time such that the absence of subjective sleepiness is not a reliable means of ruling out OSA (**Table 73.2**).[51]

OSA is a risk factor for stroke independently of sex, body mass index (BMI), diabetes, and hypertension, at least in men.[52–54] Hypothyroidism, acromegaly and chronic renal failure may also be associated with OSA.[55–58]

TABLE 73.2 Physiological definitions in obstructive sleep apnoea

Obstructive sleep apnoea/hypopnoea (OSAH)	Obstructive sleep apnoea/hypopnoea syndrome (OSAHS)
Apnoea: • Absence of breathing for at least 10 seconds **Hypopnoea:** • 30% reduction in breathing amplitude with at least 3% oxygen desaturation; or • Respiratory-related arousal (RERA) via EEG or nasal flow limitation pattern **Apnoea-hypopnoea index (AHI)** is the hourly rate of apnoeas plus hypopnoeas: • AHI <5 – normal • AHI 5–15 – mild OSAH • AHI 16–30 – moderate OSAH • AHI >30 – severe OSAH	**Comprises:** >5 obstructed breaths/hour AND excessive daytime sleepiness not better explained by other factors OR 2 or more of the following: • choking or gasping in sleep • recurrent awakenings • unrefreshed sleep • daytime fatigue • impaired concentration

A number of studies have reported impaired glucose metabolism in OSA patients, independent of obesity, although possibly related to visceral obesity, and with prevalence 9 times more in subjects with OSA than controls matched for BMI.[59–71] Insulin resistance may develop due to the effect of intermittent hypoxia and increased sympathetic activity.[59, 62, 70] Cross-sectional studies show a strong association of diabetes mellitus with OSA, but in longitudinal studies, incidence of diabetes was not related to the initial severity of OSA.[70, 72] These cardiovascular and metabolic associations may, in addition to road traffic and work related accidents, contribute to the increased morbidity and mortality associated with OSA, and the reduction in mortality seen in uncontrolled treatment studies using continuous positive airway pressure (CPAP).

Central sleep apnoea (CSA)

CSA comprises recurrent episodes of apnoea during sleep despite a patent airway (**Figure 73.4**). CSA may be associated with periodic breathing in left ventricular cardiac failure with Cheyne-Stokes respiration (CSR) in which there is temporary loss of ventilatory effort or unstable ventilatory control (CSR-CSA). This may have an adverse effect on cardiac prognosis and mortality as it is associated with sympathetic activation, ventricular ectopy and atrial fibrillation. Central sleep apnoea, right ventricular dysfunction, and low diastolic BP are predictors of mortality in systolic heart failure.[47, 73] CSA may develop in subjects at high altitude and those with neurological disorders, autonomic dysfunction or narcotic opiate drug toxicity even at therapeutic dosage.[74–76] CSA may also occur with OSA in patients with nasal obstruction or after treatment with continuous positive airways pressure (CPAP) which reduces $paCO_2$.[79] Management involves treatment of the underlying condition, and continuous positive airway pressure and oxygen may be used.[77–79]

Sleep-related hypoventilation disorders

Obesity hypoventilation syndrome (OHS) is the combination of obesity (BMI 30 kg/m^2), with hypoxia during sleep, and hypercapnia during the day, due to hypoventilation. About one third of all people with morbid obesity (a BMI exceeding 40 kg/m^2) have elevated carbon dioxide levels in the blood.[80, 81] Typical clinical features include obesity, excessive daytime sleepiness, a plethoric complexion, cyanosis, and evidence of right heart failure including peripheral oedema. Surprisingly, patients may not complain of dyspnoea, despite obvious hypoxemia. Almost all subjects with OHS will also have OSAS as an overlap syndrome.[81] Alternative explanations for hypoventilation must be excluded including use of narcotics, severe obstructive or interstitial lung disease, kyphoscoliosis, severe hypothyroidism, neuromuscular disease and congenital central hypoventilation syndrome.[82]

Overlap syndromes

OSA commonly coincides with Chronic Obstructive Pulmonary Disease (COPD), and OHS, and those with COPD may have more severe nocturnal oxygen desaturation, and considerably greater risk of death.[83, 84] Features of cor pulmonale and pulmonary hypertension may be prominent. OSA may also coincide with narcolepsy, and may be a trigger for non-respiratory sleep disorders including sleep-walking and parasomnias.[83–87]

Assessment of sleep breathing disorders

A structured assessment and screening of patients with associated comorbidities will identify people with high probability for sleep breathing disorders. Reporting of apnoea by the bed partner has been more predictive of sleep apnoea than snoring alone.[88] Validated screening questionnaires for OSAS include the The Epworth Sleepiness scale score (**Table 73.1**) and the STOP-BANG questionnaire (**Box 73.3**) which has proved useful in preoperative anaesthetic risk assessment.[21, 89, 90]

Examination may reveal obesity (in 70% of patients with obstructive sleep apnoea), with BMI >30, often with increased neck circumference (often > 40 cm) and waist circumference (men > 94 cm; women > 80 cm).[91, 92] Some patients may have nasal airway obstruction (deviated nasal septum, rhinitis or polyps), or enlarged soft palate,

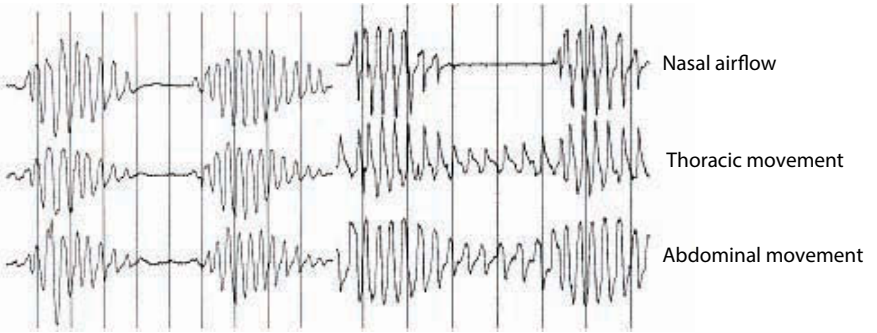

Figure 73.4 (a) Central apnoea with absence of airflow, thoracic and abdominal movement. **(b)** Obstructive apnoea with absence of airflow, but presence of thoracic and abdominal respiratory movement.

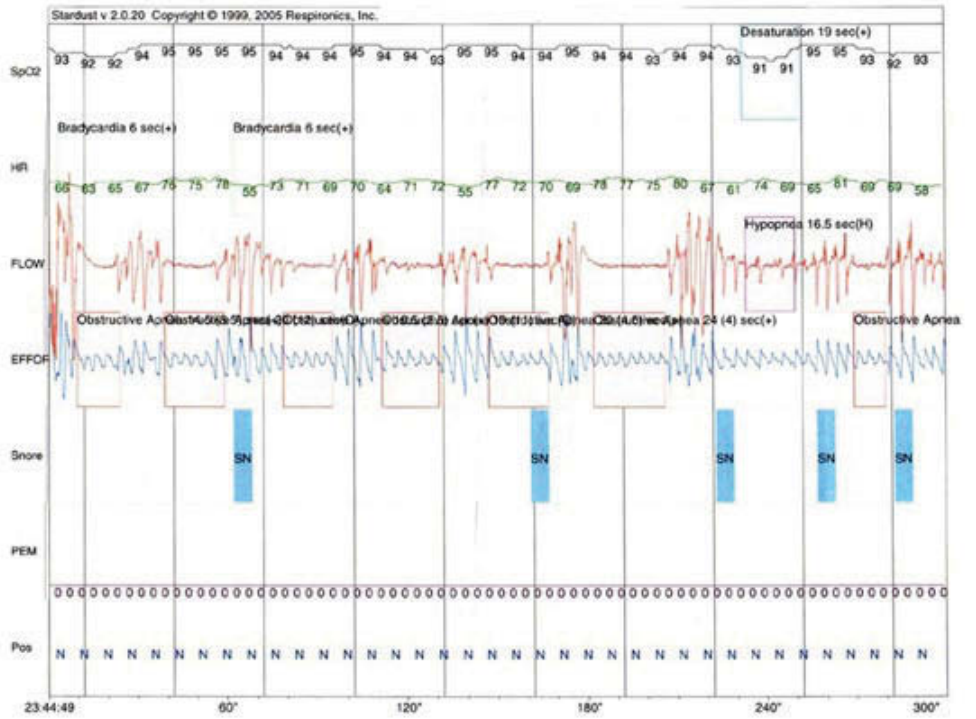

Figure 73.5. Cardio-respiratory polygraphy report. Episodic cessation of nasal airflow (FLOW) is associated with continued thoracic respiration (EFFORT) and is followed by transient fall in oxygen saturation (SpO_2). Heart rate (HR) slows following apnoeas and increases after return of respiration.

tonsils or uvula. Signs of cor pulmonale may occasionally be present including ankle swelling.

Physiological investigation of sleep-related breathing disorders

Cardio-respiratory polygraphy (multi-channel portable or ambulatory monitoring) allows diagnosis of sleep apnoea, classification, and assessment of severity in most patients with typical OSA in a home or inpatient setting.[93, 94] OSA is detected as absence of nasal airflow with persistence of chest and abdominal respiratory effort. using nasal airflow, chest and abdominal sensors, to measure respiration, producing an apnoea-hypopnoea index (AHI) (**Figure 73.5**). Oximetry in OSA typically shows a normal baseline oxygen saturation with intermittent dips and 4% oxygen desaturation index (ODI) of more than 10 per hour, together with heart rate variability (**Figure 73.6**). Overnight oximetry alone is relatively specific, but insensitive for OSA such that absence or relative paucity of oximetry dips does not exclude sleep apnoea.[95] Periods of low baseline oxygen saturation suggest other causes of respiratory failure including sleep hypoventilation syndromes and COPD which may be concurrent with OSA as overlap syndromes (**Figure 73.7**). Oxygen desaturation may occur due to other respiratory and cardiac disorders and expert interpretation is essential. In UARS apnoeas and hypopnoeas are absent or low in number, but a diagnosis may be made using a nasal cannula and pressure transducer to measure inspiratory airflow limitation, and detect a pattern known to be associated with respiratory related arousals (RERA) on EEG.[22]

Full PSG may be required in complex sleep disorders including cases of possible OSA which may overlap with comorbidities including cardiac failure, COPD, upper airway resistance, obesity hypoventilation syndrome or non-respiratory sleep disorders including periodic limb movement and narcolepsy.[96] Full PSG adds an electroencephalogram (EEG) for sleep staging and video recording and may help to differentiate OSA from nocturnal epilepsy, or demonstrate OSA as a trigger for sleepwalking or other sleep behavioural disorders (parasomnias). In UARS, multiple RERAs may be seen on EEG in association with nasal flow limitations, and if an oesophageal probe is used, progressive elevation of esophageal pressure fluctuations (Pes) terminating in arousals.[37]

Management of sleep breathing disorders

General measures for treatment of sleep breathing disorders include behavioural modification and lifestyle advice comprising weight control, elevation of the bed head, and avoidance of supine posture, alcohol, tobacco, sedatives and narcotics.[96, 97] Significant weight loss has been associated with a 'cure' rate of 10–20% in OSAHS.[98–101] Treatment of nasal congestion using nasal steroids may be helpful, especially if there is nasal obstruction or upper airway resistance due to rhinitis. Driving should be avoided if excessively sleepy and subjects with OSAS must inform the relevant driving licencing authority of the diagnosis. Driving may be allowed if symptoms are controlled on treatment, with confirmation by medical opinion.

A range of interventions may be employed in the treatment of sleep breathing disorders, including weight management, nasal continuous positive airway pressure (CPAP), oral appliance therapy and surgical intervention in OSAHS, as well as non-invasive bi-level ventilation in sleep hypoventilation syndromes, and these are dealt with in detail in other chapters.[96–112]

BOX 73.3 Stop-BANG questionnaire as a screening tool for OSA

S 'Do you snore loudly (louder than talking or heard through closed doors)?'
T 'Do you often feel tired, fatigued, or sleepy during daytime?'
O 'Has anyone observed you stop breathing during your sleep?'
P 'Do you have or are you being treated for high blood pressure?'
B Does the patient have a BMI of more than 35?
A Is the patient older than 50?
N Is the patient's neck circumference greater than 40 cm?
G Is the patient male?

Scoring: ≥3 high risk of OSA
<3 low risk of OSA

CENTRAL DISORDERS OF HYPERSOMNOLENCE

Narcolepsy and cataplexy

Narcolepsy is a condition in which subjects develop severe, often unavoidable chronic sleepiness, with fragmented sleep and frequent awakenings at night, often beginning in early adolescence or adult life. Its prevalence is 1 in 2500, but most are undiagnosed. Consequent problems include avoidance of social or emotional situations, exam failures, few work opportunities, marital difficulties, low self-esteem and depression.

Narcolepsy may be associated with other sleep disorders including restless legs syndrome (RLS) and periodic limb movement syndrome (PLMS), parasomnias, snoring, OSA and disorders of appetite and mood.[22] Sleepiness is usually severe, with ESS score often above 15. Subjects often develop hypnagogic (sleep onset) or hypnopompic (sleep offset) hallucinations and sleep onset/offset paralysis due to REM intrusion into wakefulness while falling asleep or

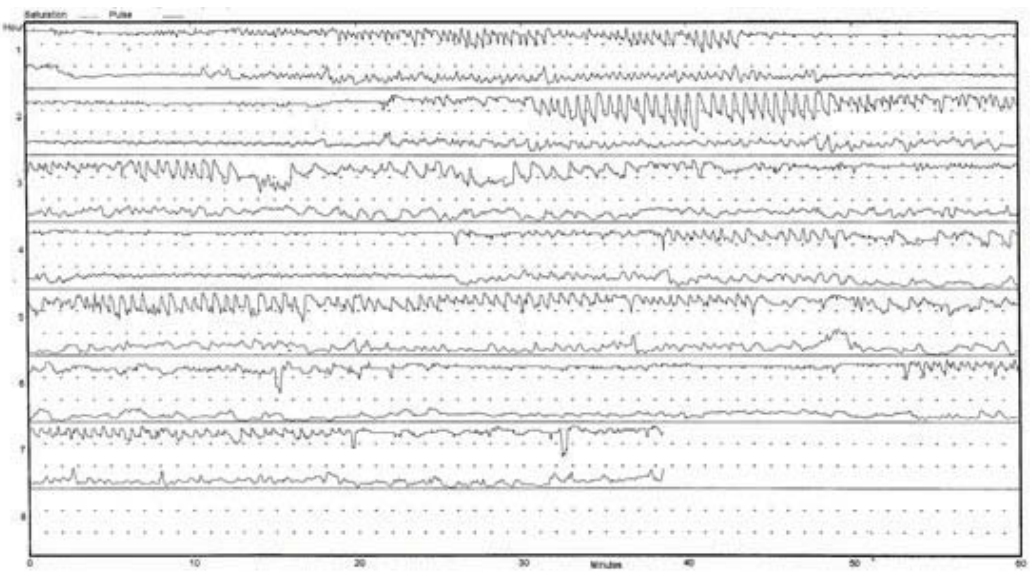

Figure 73.6 Overnight oximetry in OSA. Each horizontal band shows 1 hour of recording of oxygen saturation (above) and heart rate (below). There are frequent falls in oxygen saturation (>4%) with return to normal baseline, and associated heart rate variability.

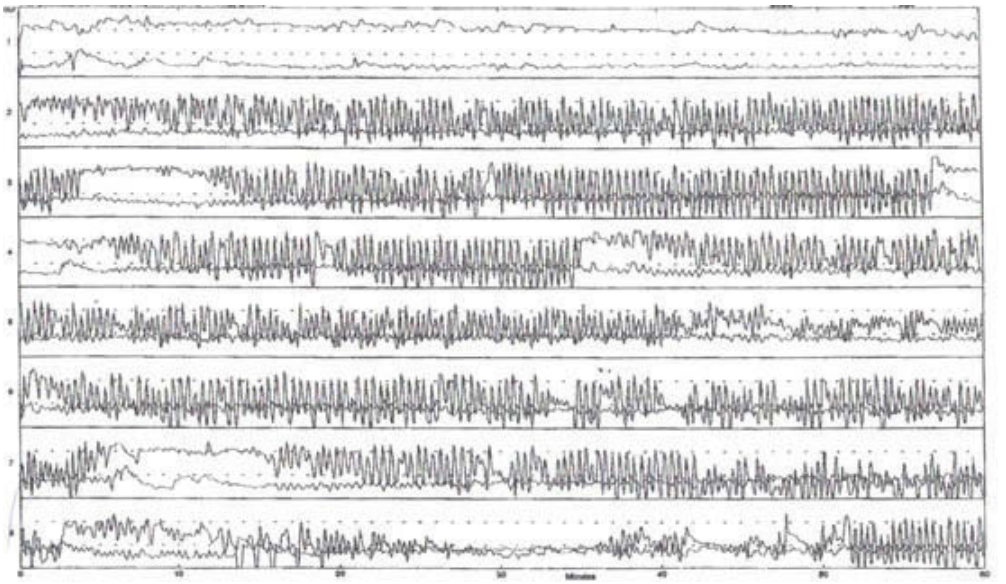

Figure 73.7 Overnight oximetry in obstructive sleep apnoea with obesity hypoventilation (overlap syndrome). Each horizontal band shows 1 hour of recording of oxygen saturation (above) and heart rate (below). There are frequent falls in oxygen saturation (>4%) but periods of low baseline oxygen saturation.

on waking. These are, however, non-specific features of sleep deprivation and they may occur in other conditions of significant sleep loss including shift work or sleep apnoea.

Cataplexy develops in 60% of subjects. During wakefulness, REM intrusions cause sudden episodes of bilateral muscle weakness leading to partial or complete collapse and often triggered by strong emotions such as laughter, anger or excitement. Episodes last 1–2 minutes and are not associated with impairment of consciousness at onset.[22, 113]

Narcolepsy is usually sporadic, and possibly auto-immune or related to brain injury, but genetic factors play an important role with a 40-fold risk in first-degree relatives. Most narcoleptics (50–90%) have HLA DR2 or DQB1*0602 antibody subtypes. The pathophysiology of classical narcolepsy involves a deficiency of the hypothalamic excitatory neuropeptide hypocretin (orexin). This is required to stabilize the hypothalamic sleep/wake switch between sleep promotion (ventro-lateral pre-optic nucleus) and wake promotion (tubero-mamillary nucleus). CSF examination reveals absence of hypocretin (orexin) in 90% of subjects.[114]

PSG may show a short REM latency 5–10 mins (in 50%). Frequent intrusions of REM cause fragmentation of deeper sleep, although total sleep time and time in REM are normal. A daytime MSLT may show sleep-onset REM (SOREM) episodes.[115]

A diagnosis of classical narcolepsy (Type 1) requires either cerebrospinal fluid hypocretin-1 deficiency (<110 pg/mL or less than one-third of the normative values with the same standardized assay) or a mean latency of <8 min with evidence of two SOREMPs on MSLT, (or one SOREMP on PSG and one or more on MSLT) and clear cataplexy. Narcolepsy Type 2 maintains the same MSLT requirements but cataplexy must be absent and cerebrospinal fluid hypocretin-1 levels, if measured, must not meet the narcolepsy Type 1 criterion.[22]

The differential diagnosis of narcolepsy includes OSA, depression, REM deprivation and drug toxicity, while the differential diagnosis of cataplexy includes epilepsy (especially gelastic and atonic), vertebro-basilar insufficiency, cardiac dysrhythmias, drop attacks, myasthenia gravis, periodic paralysis, faints, gelastic syncope and hysteria.

Management of narcolepsy includes planned napping, sleep hygiene and psychosocial support. Sleepiness may respond to stimulants including modafinil, dexamphetamine or methylphenidate. Cataplexy may respond to REM sleep-suppressing medications including tricyclic and SSRI antidepressants. Sodium oxybate or pitolisant may control cataplexy as well as sleep fragmentation and excessive daytime sleepiness.

Hypersomnia may also be idiopathic or due to medical or psychiatric disorders including Kleine-Levin Syndrome. Behaviourally induced insufficient sleep can be excluded by actigraphy or sleep logs to record wake and sleep using body movements over periods of days.

CIRCADIAN RHYTHM SLEEP-WAKE DISORDERS

Circadian rhythm problems include jetlag, shift work sleep disorder and advanced or delayed sleep phase syndromes. Delayed sleep phase is not uncommon in younger subjects who may be genetically predisposed to be 'night-owls', with difficulty in rising and excessive morning sleepiness. Symptoms may be incorrectly attributed to insomnia or depression, although these may be true comorbidities. Assessments are made using sleep diaries and actigraphy to record wake and sleep using body movements over periods of days. Treatment involves advancing sleep onset by use of evening melatonin and morning bright light therapy.[116]

PARASOMNIAS

The term parasomnia encompasses sleep-related behaviours, emotions, perceptions, dreaming and autonomic

nervous system events during entry into sleep, within sleep or during arousals from sleep.[22] Parasomnias may be occur in non-REM and REM sleep.

Non-REM parasomnias

Non-REM parasomnias include sleepwalking, sleep talking, confusional arousals, sleep terrors, sleep-related nocturnal eating disorder and catathrenia (groaning). Instinctual behaviours, including violence and sexual activity, may be released inappropriately.[117] Arousals in sleep leave the individual in a state of incomplete awakening, with inappropriate responsiveness. Higher cognitive functions and social inhibitions may be absent or impaired and primitive behaviours may appear unexpectedly with partial or complete amnesia.[22, 117]

Predisposition to non-REM parasomnias may be based on genetic susceptibility with a familial pattern. A priming factor may trigger an episode, for example sleep deprivation, situational stress, medications, fever, alcohol, sleep-disordered breathing (e.g. OSA), PLMS, noise and touch.[118]

Assessment requires a full medical and sleep history, neuropsychiatric and psychometric examination and EEG. PSG may reveal precipitating and modulating factors including OSA or PLMS.

Treatment comprises reassurance and explanation of the mechanisms and potentiating factors, and treatment of confirmed priming or trigger factors. Counselling and psychological intervention with cognitive behavioural therapy may have a role. Drug therapy is usually avoided in the absence of behaviour that causes violence to the subject or others. In that event, clonazepam or other sedatives are usually advised until the parasomnia resolves in the hope that a normal sleep pattern will return without prolonged drug therapy. Subjects with non-REM parasomnia (e.g. sleepwalking) may expect occasional relapse if under particular emotional stress, physically ill with fever or other physical stress, or under the influence of alcohol, drugs or other toxins.

REM-related parasomnias

REM-related parasomnias include REM sleep behaviour disorder (RBD), nightmares and recurrent isolated sleep paralysis. RBD involves vocalization or dream enactment during REM sleep, without the normal loss of muscle tone. The dream-enacting behaviours are usually non-directed and may include punching, kicking, leaping or jumping from bed while asleep. Subjects may recall the dream that corresponds to the physical activity, sometimes vividly or as nightmares. Abnormal sleep movements may lead to injuries include bruising, lacerations, fractures and subdural haematomas.[119] Subjects are often middle-aged or older at the time of presentation and RBD may be a precursor of degenerative brain disease or Parkinson's disease.

Acute RBD may follow withdrawal of alcohol or drugs including pentazocine, nitrazepam, tricyclic antidepressants or caffeine. Chronic RBD may follow toxicity from tricyclic or SSRI antidepressants, seligiline or anticolinergics. Chronic RBD may also be associated with neurodegenerative conditions, synucleinopathies (Parkinson's disease, multiple system atrophy and dementia with Lewy bodies) and other neurological disorders including multiple sclerosis, Guillaine-Barre syndrome, Shy-Drager syndrome, Arnold-Chiari malformation, Alzheimer's dementia, ischaemic strokes and narcolepsy.[120]

RBD may reflect dysfunction in the brainstem circuitry and the dorsolateral pontine tegmentum mechanisms responsible for the normal suppression of muscle tone and paralysis in REM sleep. PSG may show persistence of EMG tone in REM sleep, absence of seizure activity, and gross complex body movements that correspond to dream mentation.[121]

Management of REM-related parasomnias comprises removal of potential drug or other triggers. Drug therapies including clonazepam or other benzodiazepines, and melatonin may be helpful, avoiding the potential risks of opiate sedation.[122, 123]

Epilepsy may co-exist with, or mimic, sleep disorders. Sleep deprivation can increase the risk of seizure activity and seizures can affect the sleep-wake cycle. Nocturnal frontal lobe epilepsy may occur only during sleep, and can present with bizarre movements such that differentiation from parasomnia may be difficult, and expert assessment is required.[124]

SLEEP-RELATED MOVEMENT DISORDERS

Sleep-related movement disorders include restless legs syndrome (RLS), periodic limb movement disorder (PLMD) and sleep related bruxism (teeth grinding).

RLS is a clinical diagnosis, characterized by symptoms including unpleasant, creeping or crawling sensations deep within the lower legs, but sometimes in the upper limbs. It occurs only after rest, and is diurnal, becoming most severe in the late evening. There is an almost irresistible urge to move the legs, with relief on movement such as walking.[125]

The prevalence of RLS is 5–10% and it is slightly more common in women. It occurs at any age, but commonest onset is in those aged in the 5th and 6th decades. 60–80% of cases are familial with autosomal dominance and variable penetrance.

More than 80% of RLS patients have PLM in sleep (PLMS), although not all PLMS patients have RLS. PLMS comprises involuntary rhythmic muscular jerks, with extension of the great toe and dorsiflexion of ankles or other joints. PSG demonstrates a series of 4 of more consecutive movements lasting 0.5–20 seconds with an interval of 4–90 seconds. PLMS at a rate of more than 5 per hour, associated with arousals, can present as insomnia, excessive sleepiness or movements that wake the patient or bed-partner.[126, 127]

PLMD may be diagnosed when, in the absence of RLS, the frequency of PLMs is >15 per hour accompanied by clinical sleep disturbance or other functional impairment.

Predisposing factors for RLS/PLMS include some genetic variants, positive family history and female sex. Precipitating factors include iron deficiency, often related to pregnancy, menorrhagia, chronic renal failure or rheumatoid arthritis. RLS/PLMS may be precipitated or worsened by prolonged immobility, caffeine, nicotine,

and alcohol, and also by anti-depressants and dopamine antagonists including anti-psychotic and anti-emetics.

PSG can reveal periodic limb movement and associated arousals. Physiological changes include microarousals with fragmentation of normal sleep architecture, reduced time asleep, and frequent wakening.

The pathology in PLMS may involve defective dopaminergic neurotransmission and abnormal iron uptake and storage in the substantia nigra where it is a dopamine substrate.[128]

Management is by avoidance of caffeine, tobacco, and alcohol stimulants, as well as regular daily exercise, good sleep hygiene and avoidance of medicines that trigger symptoms. Prolonged iron therapy is indicated if serum ferritin is low or low normal (< 50 ng/ml) even if haemoglobin is normal. Treatment options include gabapentin, pregabalin, or dopaminergic agonists (rotigotine, ropinirole, pramipexole, L-dopa). Benzodiazepines, opiates and anticonvulsants can also be effective.

SUMMARY

Sleep disorders are common causes of morbidity and mortality, affecting the population beyond those with the condition. The presentation of sleep disorders is myriad due to complex pathophysiological mechanisms, such that important treatable conditions are often unrecognized. Greater awareness and screening of those at risk, including those with associated comorbidities, and those undergoing anaesthetic assessment and surgery, will lead to improved diagnosis and management outcomes.

KEY POINTS

- Excessive daytime sleepiness that is severe or unavoidable is suggestive of narcolepsy (sleep attacks), especially if associated with cataplexy.
- Excessive sleepiness may be due to multiple sleep disorders (e.g. narcolepsy and sleep apnoea, both often associated with excessive weight).
- Sleep Maintenance Insomnia associated with excessive daytime sleepiness suggests an underlying primary sleep disorder as a cause of arousals (e.g. sleep apnoea or periodic limb movement).
- Sleep initiation insomnia without excessive daytime sleepiness suggests adequate sleep but a possible psychological cause or misperception of actual sleep.
- RLS is a clinical diagnosis based on symptoms, whereas diagnosis of periodic limb movement requires PSG.
- Sleepwalking (non-REM parasomnia) is common, and often associated with a family or previous childhood history and complex stereotypical movement (e.g. talking).
- Parasomnias need careful differentiation from seizure disorders and degenerative brain disease, especially if movements are bizarre.
- Consider obstructive sleep apnoea in subjects with snoring, witnessed apnoeas, nocturnal choking or snorting, and excessive daytime sleepiness.
- Sleep maintenance insomnia with wakings and arousals associated with excessive daytime sleepiness suggests a possible underlying sleep disorder, e.g. sleep apnoea or periodic limb movement.
- Consider nocturnal hypoventilation in subjects with morning headache, otherwise unexplained ankle swelling (reflecting cor pulmonale and pulmonary hypertension).
- Screen for obstructive sleep apnoea prior to anaesthesia and surgery in subjects at high risk including those with retrognathia, craniofacial abnormalities, obesity, hypertension, diabetes mellitus Type 2, cardiovascular disease and cerebrovascular disease (e.g. stroke).

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CHAPTER 74

OBSTRUCTIVE SLEEP APNOEA: MEDICAL MANAGEMENT

Dev Banerjee

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SEARCH STRATEGY

Data in this chapter may be updated by a Medline search using the keywords: obstructive sleep apn(o)ea, excessive daytime sleepiness, continuous positive airway pressure, polysomnography and road traffic accidents.

INTRODUCTION

Obstructive sleep apnoea (OSA) can be regarded as a condition characterized by repetitive upper airway obstruction leading to sleep fragmentation, cardiovascular stimulation and oxygen desaturation during sleep. These together lead to symptoms such as snoring, unrefreshing sleep, excessive daytime sleepiness (EDS) and the increased risk of cardiovascular disease, hypertension, insulin resistance and road traffic accidents. Any individual with time may oscillate within a spectrum of sleep disordered breathing, from intermittent simple snoring, to chronic heavy snoring, to upper airway resistance syndrome (UARS), to mild OSA, to moderate OSA, to severe OSA or to obesity hypoventilation syndrome (OHS). OSA is characterized by complete breath-holds (apnoeas) and partial breath-holds (hypopnoeas) – scientific physiological descriptions are presented in Chapter 73, Physiology of sleep and sleep disorders. With the present obesity epidemic, ear, nose and throat (ENT), hypertension, obesity, diabetes and sleep specialists are witnessing a large increase in the prevalence of OSA in their practice. This chapter describes the medical management of OSA, especially associated comorbidities, diagnosis and continuous positive airway pressure (CPAP), all relevant to the work environment of ENT specialists. Mandibular devices are not discussed in this chapter and are described in Chapter 75, The surgical management of snoring.

EPIDEMIOLOGY, RISK FACTORS AND ASSOCIATED MEDICAL CONDITIONS

Earlier studies of the prevalence of OSA in society (Wisconsin Sleep Cohort Study) estimated that 4% of men and 2% of women had OSA with sleepiness,[1] also known as obstructive sleep apnoea hypopnoea syndrome (OSAHS). However, since then, the prevalence of obesity has been increasing in all age groups. In the UK, it is estimated that 26% of adults are obese (body mass index (BMI) $\geq 30\,kg/m^2$).[2] Further analysis of the epidemiology of OSA has suggested the prevalence of OSAHS is around 5% in a given population,[3] and it is likely this will increase with time. The exact incidence of OSA without EDS is unclear, as this population is less likely to seek medical input in the primary care setting. The prevalence differences between men and women are intriguing and the exact reason why OSA is more common and more severe in men is not fully understood. Men generally have a higher prevalence of OSA than women but the effects of menopause, pregnancy and the presence of polycystic ovarian syndrome have been shown to increase the risk of OSA in women.[4] Various mechanisms may exist, including body fat distribution, cranio-facial differences, and the role of female hormones, over and beyond simply BMI.[5] There is increasing evidence that ethnic differences do exist and people of oriental Chinese origin have a greater risk of

developing OSA at a lower level of obesity compared to European Caucasians. Cranio-facial differences may explain this phenomenon.[6] There is little information, however, on the prevalence of sleep disordered breathing in the South Asian population in the UK compared to the indigenous population in South Asia.

Obesity is recognized as an important risk factor for OSA. The prevalence of OSA rises with obesity[7] and it is estimated that up to 75% of those with a BMI above 40 kg/m^2 have OSA.[8] The exact relationship between obesity and OSA is not well understood, however, and is probably multifactorial. Factors including BMI, neck soft tissue mass, parapharyngeal and lingual adipose deposition, and body fat distribution all play a role. Any weight gain is not necessarily wholly adipose and an increase in soft tissue mass around the airway may be more crucial. Other factors such as pharyngeal muscle tone and the biophysical compliance relationship between airway patency and critical closing pressure remain unresolved.

OSA is associated with cardiovascular disease[9–11] and clinicians treating and dealing with patients with OSA are increasingly involved in modifying cardiovascular risk in their practice. OSA is associated with an increased risk of hypertension, as shown in population studies. There is growing evidence that treating OSA will decrease blood pressure, and even modest falls in blood pressure may translate into significant modification of cardiovascular risk. Associated comorbidities such as obesity, diabetes and smoking history may cloud any direct causal relationship between OSA and cardiovascular disease and further larger longitudinal studies assessing the impact of CPAP therapy on cardiovascular outcomes, particularly coronary artery disease, are warranted.[12]

The term metabolic syndrome has been increasingly used and described in relation to OSA.[13] Metabolic syndrome encompasses a cluster of features related to obesity, diabetes and hypertension. These include waist circumference, triglyceride and glucose levels, and hypertension. There is an increased incidence of metabolic syndrome in patients with OSA.[14] With increasing evidence that OSA is associated with insulin resistance and diabetes mellitus,[15–17] it is becoming more apparent that OSA may play an important role in metabolic syndrome and diabetes mellitus.

SYMPTOMS, CLINICAL EXAMINATION AND ASSESSMENT OF EXCESSIVE DAYTIME SLEEPINESS

Symptoms associated with OSA are shown in **Box 74.1**. Clinical assessment of OSA entails a detailed history, ideally with the partner present during the consultation. The partner may be able to describe the breath-holding, associated gasping, and movement arousals (associated with the apnoeas and hypopnoeas) and may possibly display a raised level of anxiety. Many couples may express marital strife and hence it is prudent for the clinician consider their issues with compassion. Even if the patient with possible OSA is banished to the next bedroom, the witnessed apnoeas are still reportable by the pauses in the audible snoring. Some patients may have had OSA for many years and therefore become accustomed to their EDS and hence may underestimate their symptoms. An appreciation of their sleep patterns is important, as one of the commonest causes of EDS is sleep deprivation rather than sleep fragmentation (i.e. OSA).

BOX 74.1 Symptoms of obstructive sleep apnoea (OSA)

- Snoring
- Fatigue
- Witnessed breath-holds
- Gasping and choking
- Excessive daytime sleepiness
- Fragmented sleep
- Unrefreshing sleep
- Reduced alertness
- Mood changes
- Nocturia

Some will relay how EDS may affect their working lives, especially those who work with heavy machinery or drive professionally. Taking a history of road traffic accidents (RTAs), therefore, is vital. Individuals with OSA are at a higher risk of RTAs, with associated costs.[18, 19] Although individuals may not have had an RTA as a result of falling asleep at the wheel, subtle clues such as drifting across lanes, clipping the kerb, or a history of being beeped at by other drivers whilst driving are useful indicators of driving whilst sleepy.

The presence of central obesity is a particularly relevant physical finding during an OSA consult. A BMI greater than 28 kg/m^2 should increase the suspicion for OSA. Neck circumference is a useful measure; above 43 cm may be predictive. Other examination features of importance include a detailed nasal and oropharyngeal assessment, including the Mallampati score,[20] and the presence or absence of retrognathia, cranio-facial abnormalities and tonsillar hypertrophy. Information about possible associated medical conditions such as hypertension, diabetes and dyslipidaemia should always be sought during the consultation.

Unfortunately, the assessment of history and clinical findings has been shown to lack sensitivity and specificity in diagnosing OSA. It is estimated that history and examination can only predict OSAHS in 50% of patients.[21] The measurement of EDS may be subjective and objective. The commonest subjective questionnaire used is the Epworth Sleepiness Scale (ESS; see **Table 74.1**), named after the Epworth hospital, Melbourne, Australia.[22] A score above 10 (out of 24) may indicate EDS; but the ESS lacks sensitivity and specificity. Therefore, in any individual, the ESS may not on its own be very useful, but act only as a guide. It is generally not recommended that clinical decision-making is based purely on the ESS. More recently, the STOP-Bang questionnaire (**Box 74.2**) has been developed as a pre-operative screening tool to identify patients with undiagnosed OSA,[23] and has been shown to identify moderate to severe cases of OSA in the surgical population.[24]

TABLE 74.1 Epworth Sleepiness Scale (ESS)
Assesses the likelihood of an individual dozing off at the following situations (score 0 = never, 1 = slight chance, 2 = moderate chance and 3 = high chance of dozing)

Situation	Chance of dozing
Sitting and reading	
Watching TV	
Sitting inactive in a public place (e.g a theatre or a meeting)	
As a passenger in a car for an hour without a break	
Lying down to rest in the afternoon when circumstances permit	
Sitting and talking to someone	
Sitting quietly after a lunch without alcohol	
In a car, while stopped for a few minutes in traffic	
TOTAL	

BOX 74.2 STOP-Bang questionnaire – answer Yes or No

- Snoring – Do you snore loudly (louder than talking or heard through closed doors)?
- Tired – Do you often feel tired, fatigued, or sleepy during daytime?
- Observed – Has anyone observed you stop breathing during your sleep?
- Blood pressure – Do you have or are you being treated for high blood pressure?
- BMI – BMI of more than 35 kg/m^2?
- Age – Age over 50?
- Neck circumference – neck circumference greater than 40 cm?
- Gender – Gender male?

High risk of OSA (AHI > 5/hr): answering yes to three or more items

Low risk of OSA (AHI < 5/hr): answering yes to less than three items

Objective measurements of EDS include the Multiple Sleep Latency Test (MSLT), which measures how quickly an individual can fall asleep, and the Maintenance of Wakefulness Test (MWT), which measures how long an individual can stay awake. However, such diagnostic tests can only be measured if full polysomnography facilities, including EEG, are available, as without EEG, accurate assessment of wake and sleep cannot be made.

THE DIAGNOSIS OF OBSTRUCTIVE SLEEP APNOEA

Methods designed to diagnose OSA may include domiciliary single channel (overnight oximetry), domiciliary multichannel (respiratory and oximetry signals) and in-hospital full polysomnography (PSG), which includes measurement of respiratory, oximetry and sleep architecture assessment using electroencephalography (EEG), electrooculography (EOG) and electromyography (EMG) parameters. The merits of each tool are discussed below.

Overnight oximetry

This method measures variations in oxygen saturation and pulse rate during sleep. It assumes that when an individual has an apnoea or hypopnoea, the oxygen saturation falls. Once the apnoea or hypopnoea is relieved, the oxygen desaturation recovers. The falls and rises are regarded as 'oxygen dips'. The pulse oximeter is applied over the end of a digit, which is attached to a wristwatch computer that the patient wears during the night. This is where the data are collected. For convenience, the device can be worn at home. More sophisticated software products provide pulse rate variability (e.g. the number of pulse rises of over six beats per minute averaged out per hour), which would reflect autonomic cardiovascular changes during arousals as a result of apnoeas and hypopnoeas. However, pulse rate variability can only be analyzed in the presence of sinus rhythm rather than in patients with atrial fibrillation.

In the UK, some sleep clinicians use oximetry alone as a screen for OSA. It is standard practice that a 'dip' of 4% oxygen saturation (e.g. from 94% to 90%) is regarded as more meaningful than a 2% or a 3% dip. An oxygen desaturation index (ODI) (i.e. the number of times the oxygen saturation falls by 4% averaged out per hour) of more than 15 per hour may be suggestive of OSA. The presence of other associated features that are measured that may lean towards a diagnosis of OSA in the presence of a 'positive' oximeter result include EDS (ESS > 10), obesity (BMI > 28 kg/m^2), and the presence of other comorbidities (e.g. hypertension, coronary artery disease, metabolic syndrome and diabetes mellitus). However, an ODI > 15 per hour can only be used if the resting saturation of oxygen is above 90% and there is an absence of obstructive airway disease. **Figures 74.1** and **74.2** show a classic case of repetitive oxygen desaturation during sleep, typical of OSA.

Although studies using overnight oximetry as a screening tool for OSA have shown good specificity and positive predictive value, this test is associated with poor sensitivity and negative predictive value.[25] In other words, overnight oximetry may miss patients with OSA who do not desaturate, but in the presence of a positive result, the oximetry can be a useful screen. However, an abnormal ODI may underestimate the true severity of OSA, as demonstrated in **Figures 74.3** and **74.4**. Generally it is accepted that young, less obese patients may not have oxygen desaturations in the presence of apnoeas and hypopnoeas and therefore will be missed by oximetry. Mechanisms why some patients desaturate and some do not is unclear but it may be related to lung volumes, functional residual capacity or central respiratory response to apnoeas (i.e. if an arousal response to airway obstruction is blunted then the individual is more likely to hypoventilate and desaturate). It is recommended that, if the ODI is less than 15 oxygen desaturations ('dips') per hour, but there is the presence of EDS, obesity or existing comorbidity, then a further

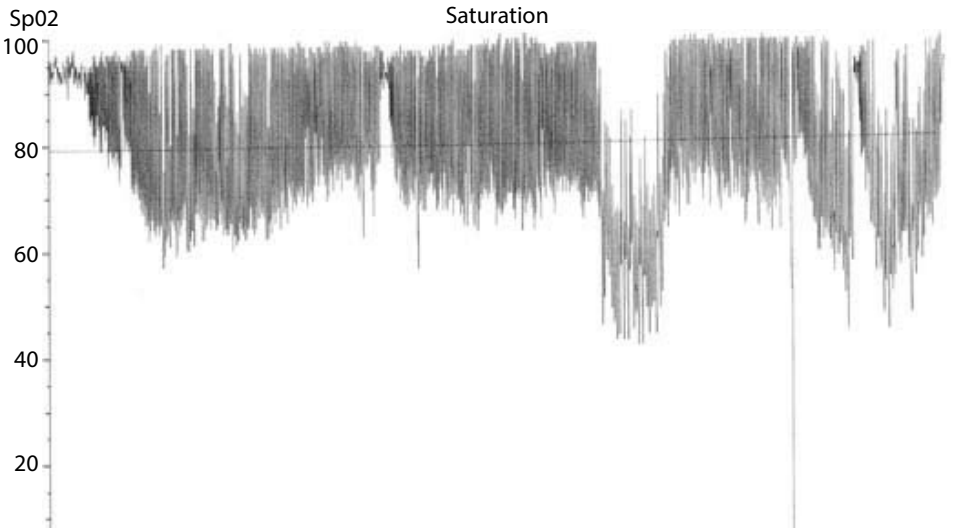

Figure 74.1 A patient with an oxygen desaturation index (ODI) of 55 4% oxygen dips per hour. The oximetry trace shows the whole night data. Minimum oxygen saturation is approximately 45%.

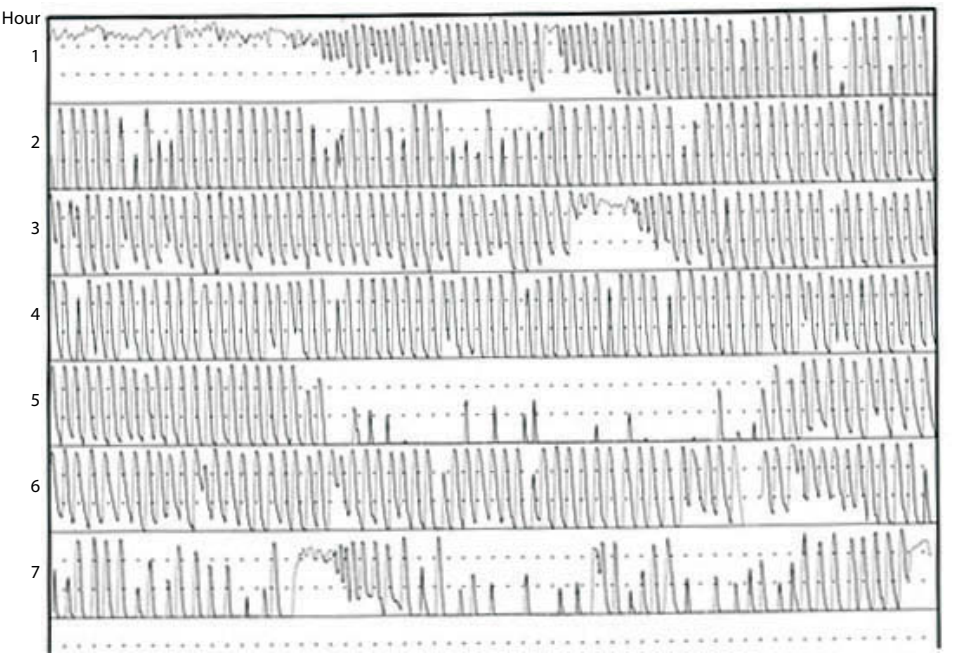

Figure 74.2 The same patient as in Figure 74.1, with a close up of the oximetry trace demonstrating oxygen dips. X axis is one hour. Y axis is 70–100% saturations. Note the marked repetitive desaturations of oxygen, typical of OSA. Occasional dips are below 70%.

referral for multichannel assessment of respiration is recommended. It is not advocated that a trial of CPAP be carried out in those where the diagnosis and severity of OSA s in question following a negative oximeter study.

Home multichannel testing

The advantages of home overnight respiratory monitoring over in-hospital studies are multiple. They include better patient comfort, cost savings and prevention of hospital admission, and allow quicker data analysis. Disadvantages include sensor failure at home and loss of signal (which may lead to repeat studies). Fewer channels will inevitably result in less available information. In particular, home monitoring without EEG will not determine when the patient is asleep during the night. Sleep disordered breathing occurs during sleep, and it may be possible that without an assessment of exact sleep time, home monitoring may underestimate the severity of OSA. Some home portable kits also include EEG probes to determine sleep architecture. However, in the UK, multichannel kits that measure nasal/oral flow via a pressure cannula, chest and abdominal movements via a pressure transducer housed in a velcro belt and pulse oximetry, but not EEG activity, are the most popular. A number of such products are available on the market. A classic example of repetitive apnoeas is shown in **Figure 74.5**. The chest and abdominal belt allows the assessor to determine if the apnoeas and hypopnoeas are related to respiratory effort (during the apnoea or hypopnoea, the chest and abdominal signals still display movement) and therefore obstructive in nature, as opposed to central sleep apnoea (CSA) where there is no chest or abdominal movement or effort during apnoeas. In contrast to OSA, the apnoeas seen in CSA originate from the respiratory drive centre of the brain and may occur in patients with cerebrovascular disease or

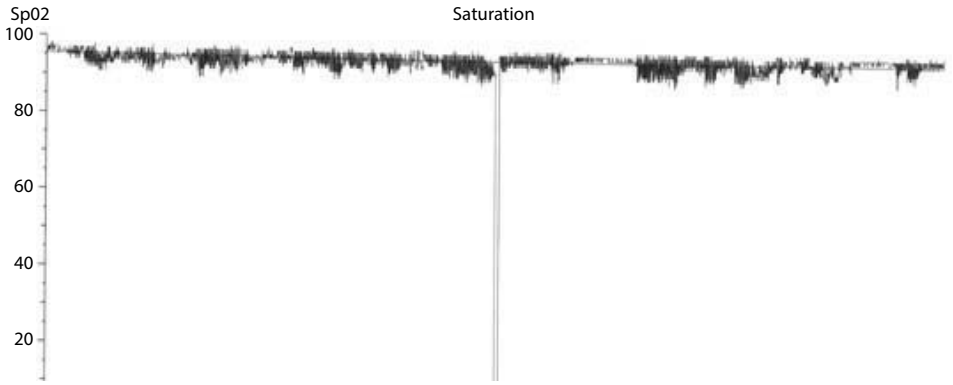

Figure 74.3 This patient has an ODI of 22 4% oxygen dips per hour, a body mass index (BMI) of 36 kg / m² and an ESS score of 6. The desaturation is not as marked as the example in Figure 74.1. The mid page reading signal to zero is an artefact.

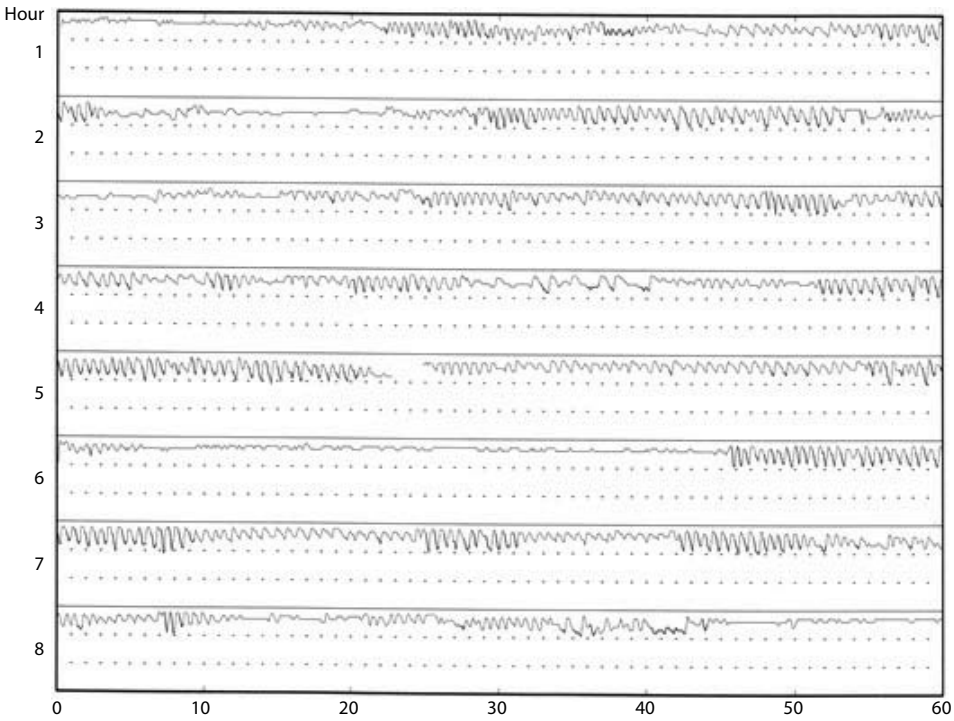

Figure 74.4 The same patient as in Figure 74.3, showing close up of oxygen dips from Figure 74.3. X axis is one hour and Y axis is 70–100% oxygen saturations. Repetitive but intermittent oxygen desaturations were seen, particularly 2% and 3% dips. The patient underwent a diagnostic polysomnography showing severe OSA, apnoea/hypopnoea index of 73 per hour. In this case the overnight oximetry on its own underestimated the true severity of OSA.

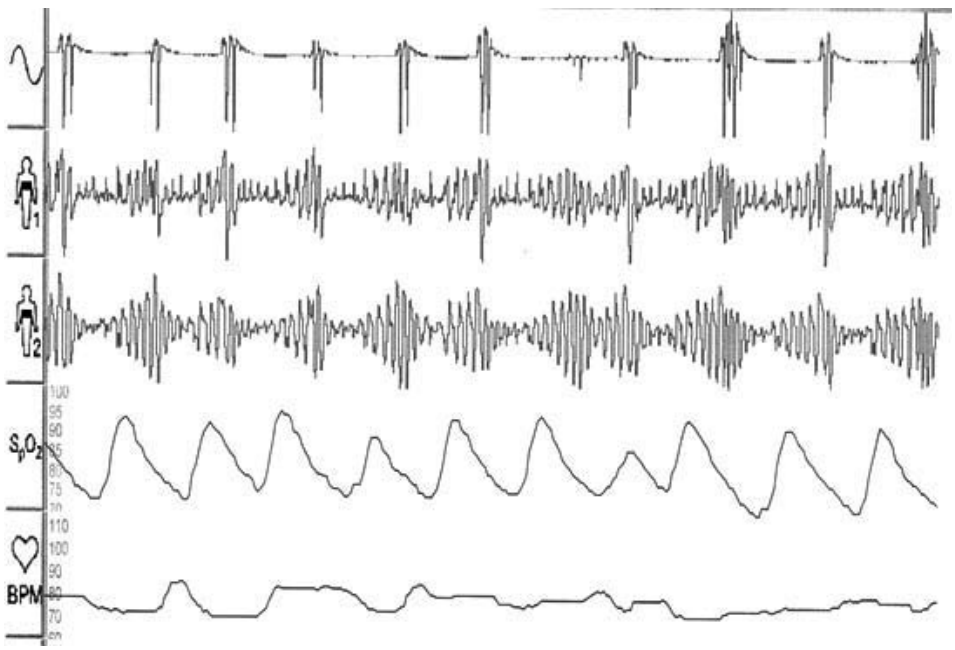

Figure 74.5 A classic example of OSA with repetitive apnoeas. X axis is 5 minutes. Top trace is oronasal cannulae flow trace, second trace is thoracic band, third trace is abdominal band, fourth trace is oxygenation and fifth trace is pulse rate. Note marked desaturations of oxygen with each apnoea, which recovers once apnoea is abolished and the pulse variability. Due to lag time effect, the nadir of oxygen saturation always follows the apnoea.

those who take regular opioids in high doses. One form of CSA known as Cheyne-Stokes respiration ('crescendo-decrescendo' chest and abdominal movements) is more common in patients with heart failure. Therefore oximetry alone would not pick up the origin of apnoeas (i.e. obstructive vs central), in such patients.

Patients are taught how to attach the necessary equipment, either at home or in the hospital physiology department. The patient then either goes home wearing the equipment or reattaches it themselves later in the evening. Following overnight data collection, the equipment is returned and the data are analyzed. Whilst in most models data analysis occurs automatically, it is recommended that the data are scored by a trained clinician or technician in an attempt to reduce software mismatching of apnoeas and hypopnoeas.

An apnoea is regarded as a completed cessation of airflow (more than 90% reduction in nasal airflow/pressure signal amplitude of the pre-event baseline) for at least 10 seconds, regardless of whether there is an associated oxygen desaturation or arousal. The definition of hypopnoea varies from centre to centre but it is typically regarded as a reduction in airflow/pressure signal amplitude by 30% of pre-event baseline or more with a 3% or more oxygen desaturation, or if the event is associated with an EEG arousal. These criteria are based on the updated American Academy of Sleep Medicine (AASM) guidelines 2012[26] (these guidelines superseded the 2007 AASM guidelines[27]). If the airflow signal is missing (e.g. mouth breathing or displaced oro-nasal cannulae), amplitude changes in the thoraco and abdominal wall movement signals can still be used to determine if apnoeas or hypopnoeas are taking place. As explained above, chest wall movement – and therefore by inference, respiratory effort – is measured indirectly as changes in pressure detected by a pressure transducer worn around the chest during sleep. The changes in pressure signal are proportional to airflow and any change in signal can be regarded as a change in airflow.

Overnight polysomnography

The disadvantages of in-hospital overnight PSG compared with domiciliary multichannel testing have been stated above. However, home testing is inadequate for a cohort of more complex OSA patients. For example, some patients may need further respiratory monitoring such as transcutaneous CO_2 testing, particularly if OHS is suspected. In other cases, such as patients with neuromuscular disorders, in-hospital assessment is warranted as assisted ventilation is required. Tertiary referral sleep centres will see a variety of sleep disorders where the EEG, EOG and EMG component of the PSG are essential (e.g. narcolepsy, parasomnias and periodic leg movement syndrome). Prior to assessment, equipment is arranged by a sleep technician. The patient stays overnight at the sleep centre and most have video monitoring during the night as well. In some centres, the technician observes the signals from a central computer room during the night. This allows for troubleshooting, such as disconnected leads, but also allows more complex assessments, such as trials with assisted ventilators or titration with CPAP machines. Whether the technician stays overnight is dependent on the staffing and funding in the particular centre. In cases where the PSG is unattended, if leads do become disconnected, with the subsequent loss of signal, a repeat PSG may be necessary.

Criteria for the diagnosis of OSA

The number of apnoeas and hypopnoeas averaged out per hour of sleep is regarded as the apnoea-hypopnoea index (AHI). Some centres use the term respiratory disturbance index (RDI), which incorporates the number of apnoeas, hypopnoeas and respiratory effort related arousals (RERA). The latter are diagnosed by EEG arousals associated with respiratory effort (from intra-oesophageal pressure measurement) in the absence of apnoeas and hypopnoeas. However, as intra-oesophageal pressures are seldom used, the term AHI is more reflective of clinical practice and is most commonly used. If home respiratory monitoring testing is carried out, an estimate of the number of hours slept by the individual is necessary. A common mistake is to calculate the total number of apnoeas and hypopnoeas and then divide this number by the total number of hours of respiratory recording and not sleep time.

The severity of OSA has been defined as:

- no evidence of OSA if AHI <5 apnoeas and hypopnoeas per hour
- mild OSA if AHI ≥ 5 and <15 apnoeas and hypopnoeas per hour
- moderate OSA if AHI ≥ 15 and <30 apnoeas and hypopnoeas per hour
- severe OSA if AHI ≥ 30 apnoeas and hypopnoeas per hour.

It is important to note that these criteria do not take into account the desaturation index or the length of apnoeas and hypopnoeas.

When to treat varies from centre to centre. Most centres would not treat mild OSA without EDS and/or existing comorbidities (i.e. hypertension, cardiovascular disease, coronary artery disease, diabetes mellitus) with CPAP. Lifestyle changes, such as weight loss strategies (particularly if the BMI is greater than $25\,kg/m^2$), and/or treatment of any troublesome rhinitis are recommended. However, if patients have mild OSA with EDS and/or comorbidities, or moderate to severe OSA with or without EDS and comorbidities, then a trial with CPAP therapy may be considered.

TREATMENT – CONTINUOUS POSITIVE AIRWAY PRESSURE

Continuous positive airway pressure (CPAP) is regarded as the mainstay of OSA treatment.[28] This technique was first described in 1981[29] and since then there have been immense technological advances driven by industry.

The mode of action can be regarded as a 'pneumatic splint' whereby the air pressure generated via a tube and mask, through the nasal and/or oral passageway, prevents collapse of the pharyngeal and palatal walls, and consequently, the airway.

The equipment

CPAP machines may provide a constant positive pressure ('fixed pressure') or may vary pressure depending on the presence of apnoeas. The latter system, delivered by autoCPAP machines, relies on an algorithm set in the machine mechanics, whereby a reduction of airflow (i.e. apnoea or hypopnoea) is detected by the machine and as a result the machine generates the appropriate retrograde flow (and therefore pressure) to overcome the apnoea or hypopnoea. For this to work successfully, a closed system between the machine and the patient has to exist.

Patient preference typically determines which mask is used but when a nasal mask is chosen, patients must ensure mouth leaks are minimized. To this end, chin straps are sometimes used to keep the mouth closed. Most masks are kept in place by Velcro straps. All masks must have an expiratory port to prevent re-inhalation of expired air. All patients are reminded to clean their masks and strappings regularly, to ensure longevity. The newer machines are smaller and lighter to allow easy portability. All new machines have an internal mechanism to allow switching between 220 and 110 volts, depending on where the user is around the world. The ease of using CPAP on planes can vary from airline to airline.[30] The use of an inverter mechanism will allow CPAP usage driven from a DC battery pack. For those who suffer from nasal congestion and/or a dry mouth, a humidifier is recommended.

Setting up CPAP

Centres differ in how a patient with OSA is set up on CPAP. All centres should have educational programmes to ensure patients gain a better understanding of their illness, in order to maximize long-term CPAP compliance. Some centres use group video workshops to achieve this. CPAP set-up should be carried out by a trained technician who understands the technology and appreciates where problems may arise.

Patients differ in the level of pressure necessary to eliminate the vast majority of their apnoeas and hypopnoeas. The method of determining this opening of airway pressure differs from centre to centre. Some use a mathematical equation. One example that has shown reasonable correlation with titration studies is: predicted pressure (cm H_2O) = (0.16 × BMI) + (0.13 × NC) + (0.04 × AHI) − 5.12, where NC is neck circumference (cm).[31]

Another method of titration of CPAP used in some centres is to admit a patient for overnight diagnostic PSG. The severity and diagnosis of OSA is confirmed by PSG during the first half of the night, then CPAP is commmenced for the second half of the night. This is referred to as a 'split night' regime. However, the process needs a supervising technologist and a big disadvantage is that the true severity of OSA may not be determined during the diagnostic first half of the night. However, an advantage is that both diagnostic and CPAP titration are performed on the same night, therefore saving an extra admission. The CPAP titration technique is carried out by a technologist from the central computer room, who has video access to the patient and electronic linkage to the CPAP machine. The starting pressure is usually around 4 cm H_2O and the pressure is quickly increased until all apnoeas and hypopnoeas are eliminated. It is the aim to reach the required pressure to eliminate the majority of apnoeas and hypopnoeas within an hour, and the rest of the night is spent fine-tuning and troubleshooting, for example, mask leaks or the need for supplemental oxygen in some cases.

Another technique that is increasingly being used is to send the patient home with an autoCPAP machine. Most autoCPAP machines will collect data on compliance, leaks and pressure profile. A trial of between 7 and 14 days may allow better adjustment to the concept of CPAP rather than an autoCPAP trial of one night. Generally autoCPAP machines are more expensive than the fixed pressure machines and as a result, in the UK, funding from clinical commissioning groups (CCGs) are predominantly for fixed pressure machines. Many centres set the fixed pressure as determined by the 90th or 95th centile pressure (i.e. the blowing pressure to eliminate 90% or 95% of apnoeas and hypopnoeas) as determined by the autoCPAP data download. CPAP therapy is recommended by the National Institute for Health and Care Excellence (NICE) as the treatment of choice for moderate to severe OSA.[32] The Scottish Intercollegiate Guidelines Network (SIGN) has produced useful recommendations on the management of OSAHS in adults.[33]

Side effects

Most side effects are related to the nasal/face mask interface. Claustrophobia can be problematic in some patients. Trying different face masks, from full face, to nasal, to an interface that sits on the nostril edge (nasal pillows) may be one solution. However, with patience, education and reassurance (an experienced technician is the key here), most patients are able to alleviate such claustrophobia issues. Nasal stuffiness is a common troublesome side effect, although interface technology has improved greatly recently to reduce this. However, despite this, nasal stuffiness and coryzal illnesses can lead to poor compliance in those patients with nasal masks. Heated humidification is recommended as one solution. Cold and dry air may provoke mucus production and vasodilation in the nasal mucosa and hence humidification may potentially address this. Although nasal corticosteroids and/or corrective surgery for mucosal thickening and polyps may be considered, most sleep centre practitioners believe that a full-face mask may be a simpler solution.

Other side effects, such as skin abrasions and leaks, are usually related to poorly fitting masks. Leaks can be a

nuisance, especially if they are directed towards the eyes. The patient has to be educated that a good fit rather than a tight fit is more likely to be successful in eliminating leaks without skin and eye trauma.

Air-swallowing and pulmonary barotrauma may also occur, although the latter is very rare. Air-swallowing and subsequent gastric distension is more likely if the pressure delivery exceeds physiological oesophageal sphincter pressure (e.g. above 15 cm H_2O). The obvious remedy is to reduce the pressure.

Compliance and troubleshooting

Compliance of CPAP usage is dependent on many factors. It has been reported that by 3 years, up to 12–25% of patients will have discontinued treatment.[34] Compliance has been defined arbitrarily in the literature as usage of CPAP for more than 4 hours for at least 5 nights per week. The biggest factor that will determine long-term compliance is the improvement of symptoms soon after commencing CPAP therapy and the severity of the OSA suffered by the individual.[34] What is unclear, when faced with an individual about to commence CPAP therapy, is whether 4 hours for 5 nights per week is enough to reduce the risk of RTAs or future cardiovascular comorbidity. It is anticipated that future clinical trial data will determine this but generally all patients are encouraged to use CPAP for at least 6 hours, 7 nights per week.

It follows that adequate education, follow-up by an experience technician and motivation of the patient all influence long-term adherence to CPAP. When CPAP failure does occur, troubleshooting interface issues, addressing side effects and assessing the presence of coexisting sleep disorders (e.g. shift-work related sleepiness, narcolepsy, psychological illness or drug-induced conditions) should be considered. This latter point is particularly important as it is not uncommon for an individual to have two coexisting sleep disorders.

There have been some suggestions that autoCPAP has advantages over fixed pressure CPAP, particularly with respect to comfort, possibly by reducing the average pressure applied throughout the night. However, although this may be the case, there is no evidence that this improves compliance or symptoms of EDS compared to fixed pressure CPAP.[35] A recent systematic review of fixed pressure CPAP vs autoCPAP showed that although there was an improved compliance by 11 minutes per night (0.18 hours; 95% CI, 0.05 to 0.31 minutes; $P = 0.006$), and that ESS score improved by 0.5 (95% CI, −0.81 to −0.15; $P = 0.005$) in the autoCPAP group, the clinical importance of these small margins of improvement remain unknown, despite being statistically significant.[36] Therefore, as the treatment effects are similar between APAP and fixed CPAP, the therapy of choice will be dependent on patient preference, the cost, and issues of non-compliance. Until there are definite cost-benefits shown for autoCPAP over the fixed pressure CPAP machine, there is no justification to mass provide autoCPAP machines on the NHS in the UK at present.

ALTERNATIVE STRATEGIES TO CPAP

Bilevel positive airway pressure (sometimes known as BiPAP) devices allow specific and separate pre-set inspiratory and expiratory pressures, for example inspiratory positive airway pressure (IPAP) between 10 cm H_2O and 20 cm H_2O, and expiratory positive airway pressure (EPAP) between 5 cm H_2O and 10 cm H_2O. These devices may improve compliance in some patients who are intolerant to CPAP but should only be used in selective cases. For those who have CSA, newer devices known as adaptive servo-ventilator (ASV) have been commonly tried. It is generally recommended that such treatment should be initiated by specialist sleep centres. Other novel treatments, such as nasal EPAP devices, are being introduced as alternative therapies[37] but randomized controlled trials comparing this form of device against CPAP are still awaited.[38]

FOLLOW-UP AND LEGAL ISSUES

At the time of diagnosis of OSA, in the UK, the individual is recommended to self-inform the Driver and Vehicle Licensing Authority (DVLA), Swansea, UK, of the diagnosis. However, the DVLA recognizes only the diagnosis of 'obstructive sleep apnoea syndrome', defined by the DVLA as OSA with sleepiness, but there is no indication of how the sleepiness is qualified or quantified and therefore diagnosis is at the discretion of the diagnosing clinician. The emphasis of responsibility to inform the DVLA in the UK is placed on the patient with 'OSA syndrome' and not the sleep clinician/ENT surgeon and so on. In reality, many patients do not inform the DVLA, as in many parts of the country the treatment for OSA (CPAP) may not be available immediately. All drivers should be reminded that by law (Road Traffic Act 1998), all drivers have a duty of care when driving. However, those patients deemed to be a genuine threat to the public by continuing to drive whilst sleepy may be considered for notification by the clinician, despite this potentially breaking rules of patient confidentiality.

Follow-up CPAP clinics are aimed to determine compliance, minimize intolerance, improve symptoms (as shown by reduced sleepiness) and continue to modify cardiovascular risk factors. Follow-up PSG with CPAP is not necessary unless other sleep disorders (e.g. periodic leg movement, insomnia) are suspected. Some centres utilize a repeat overnight oximetry with CPAP, but an abnormal tracing may not necessarily differentiate poor compliance from inadequate treatment pressure. A significant increase in weight with time may lead to the appearance of snoring with the mask on and an increase in the fixed CPAP pressure may be necessary. Leaks around the mask may be caused by the mask components wearing out, but if the mask is well looked after it should last for up to a year. CPAP machines that are provided on the NHS must be electrically serviced and checked by an engineer on an annual basis by law. The equipment technically belongs to the centre that provided the machine and therefore it is the

responsibility of the centre to ensure that it is electrically safe. During servicing, the engineer will routinely download usage data from the machine and this will provide useful compliance data. Patients with moderate to severe OSA who have suboptimal compliance are challenging to the clinician, and reasons for non-compliance should be addressed. If a patient refuses treatment with CPAP, then other solutions (e.g. weight loss, mandibular devices or even surgery) may be considered. The patient should be reminded of the issues of driving with OSA without treatment. Clinical psychology approaches, particularly cognitive behavioural therapy, may also be considered.

KEY POINTS

- Obstructive sleep apnoea is becoming more and more prevalent in society as more and more individuals become obese.
- A significant proportion of individuals with obstructive sleep apnoea are however not obese and therefore the clinician should look out for airway anatomical reasons for the apnoeas.
- Obstructive sleep apnoea is commonly associated with other comorbidities such as hypertension, cardiac disease, diabetes mellitus type II and cerebrovascular disease.
- Obstructive sleep apnoea is a common reason for impaired well-being particularly impaired mood, concentration, memory, and alertness.
- There is a higher risk of fatigue-related road traffic accidents in those who have severe obstructive sleep apnoea.
- The clinician looking after an individual with obstructive sleep apnoea should be aware of the medical (CPAP), dental (mandibular advancement splint) and surgical (Ear Nose and Throat) approaches of treatment.
- Services delivering diagnostic and therapeutic patient pathways are more commonly involving a multidisciplinary and holistic approach.

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CHAPTER 75

THE SURGICAL MANAGEMENT OF SNORING AND OBSTRUCTIVE SLEEP APNOEA

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SEARCH STRATEGY

Data in this chapter may be updated by PubMed search using the keywords: snoring, OSA, UPPP, palatoplasty, coblation, laser surgery for snoring, robotic surgery for OSA and evaluation.

EPIDEMIOLOGY

Sleep-related breathing disorder (SRBD) encompasses a broad clinical spectrum of recurring partial or complete obstruction of the upper airway. This ranges from simple or primary snoring to severe obstructive sleep apnoea (OSA). Patients who have symptoms suggestive of OSA but do not have objective parameters in a sleep study confirming the condition can be classified as having upper airway resistance syndrome (UARS). These patients may have sleep fragmentation but do not have significant oxygen desaturation events or many obstructive events. A definition of apnoea, hypopnea and the apnoea-hypopnea index (AHI) is covered in Chapter 74, Obstructive sleep apnoea: medical management.

Snoring is a sound produced (usually during inspiration) by vibrations of the upper airway caused by a turbulent airflow that, in turn, is caused by varying degree of collapse of the upper airway lumen. Simple snoring is generally not associated with significant obstruction or arousals but can be linked with tiredness. It is thought that the reason for the tiredness may be that these simple snorers, in the absence of apneas, may still repeatedly wake up as there is a need to make a greater effort to overcome the airflow resistance; furthermore, they may be awakened by their partner who is being disturbed by the noise. The exact prevalence of snoring is not easy to quantify but in general it is thought that about 40% of adults snore and of these about 10% may have some degree of obstructive episodes. Men are thought to be more likely to snore than women.

OSA is thought to affect 2–4% of males and 1–2% of females, a level of prevalence comparable to Type I diabetes.[1] Basically, in OSA there is failure of dilator muscle tone of the upper airway lumen.

The morbidity and mortality related to OSA is well recognized as an independent risk factor for hypertension, cardiovascular, Type II diabetes and cerebrovascular diseases.[2] In addition, neurobehavioural morbidities of daytime sleepiness and impaired cognitive function may contribute to motor vehicle and job-related accidents.[3, 4] Overall, OSA significantly increases the risk of stroke or death from any cause; in a community-based sample, moderate to severe sleep apnoea is independently associated with a large increased risk of all-cause mortality.[5] The obesity epidemic means problems faced by health professionals in relation to OSA are only likely to increase in the immediate future.

In terms of aetiology and aggravating factors for both snoring and OSA, there is considerable similarity and overlap. In essence, the upper airway in these patients is of a relatively small size and/or narrowed. In many of these individuals it is not uncommon to encounter a multilevel obstruction. For example, an individual may have nasal congestion or obstruction secondary to deviated nasal septum or nasal polyps and may also have a crowded oropharynx as a result of hypertrophied tonsils or a lax soft palate and an elongated uvula. Nasal congestion may further contribute to the obstruction by causing mouth breathing that, in turn, accentuates palatal vibration or oscillation of pharyngeal tissue and worsening of

tongue retraction.[6] Excessive alcohol intake,[7] obesity,[8] smoking,[9] increasing age[8] and consumption of sedatives are thought to aggravate these conditions. Certain morphological features such as micrognathia or maxillary retrusion make some patients more prone to sleep-related breathing disorders.

CLINICAL PRESENTATION

It is prudent to fully evaluate a patient before imposing surgery upon them. The full evaluation would consist of a comprehensive medical history, clinical examination and assessment and special investigations to ascertain the severity and the site or sites of anatomical obstruction within the upper airway that may be responsible for the symptoms.

CLINICAL HISTORY

This is probably better obtained if the partner is present as well. Details of both nocturnal and daytime symptoms need to be addressed. As much information as possible about snoring and sleep should be gathered and could include many of the following:

- For the partner (i.e. questions that are not easy or possible for patient to answer):
  - How severe is the snoring (audible outside the room, downstairs, by next door neighbour)?
  - Does the patient snore with mouth open?
  - Is snoring positional?
  - Are there episodes of crescendo snoring, apnoea, choking or gasping?
  - Is the patient restless and are there any other limb movements?
  - Does the patient sleep walk or sleep talk?
- For the patient:
  - Do you feel that your sleep is refreshing?
  - Do you get morning headaches?
  - Do you feel tired during the daytime? (Complete Epworth Sleepiness score.)
  - Do you suffer from night sweats or palpitations?
  - Do you have vivid dreams or nightmares?
  - Do you feel that your nose is blocked?
  - Do you smoke and drink alcohol? How much?
  - Do you have any other medical problems such as high blood pressure, heart problems, diabetes, underactive thyroid gland or past history of stroke?
  - Do you feel that your cognitive functions such as concentration and memory are impaired?
  - Has your libido diminished?
  - Have you had any driving accidents?
  - What medications do you take?
  - Have you had any surgery previously? (Assess fitness or problems with general anaesthesia.)
  - Have you tried any conservative measures such as weight loss, reducing alcohol or intranasal steroid sprays?
  - Have you tried nasal strips or nasal valve dilators to improve nocturnal breathing?
  - Have you tried mandibular advancement devices to improve snoring?

CLINICAL EXAMINATION

This can quite easily be conducted in an outpatient setting, and addresses a general inspection and examination as well as specific upper airway evaluation.

Measurements of height and body weight are obtained to calculate the body mass index (BMI). The figure for BMI is derived by dividing the body mass in kilograms divided by the square of the height in metres. Values of BMI should take factors such as body frame and ethnic difference into account. In general, however, BMI values between 20–25 are considered as being normal, between 25–30 as being overweight and more than 30 as being obese.[10] Higher values would be categorized as being premorbid or morbid obesity. Neck collar size measurement is useful as it has been suggested that there is higher chance of OSA in patients with a collar size greater than 17 inches.[11] On general inspection one ought to be on the lookout for craniofacial or facial skeletal framework deformity such as seen in patients with acromegaly, maxillary retrusion or micrognathia.

Specific upper airway evaluation should commence with the examination of the nose and nasal cavity. External nasal deformity and abnormal nasal valve function can both contribute to difficulty in breathing and upper airway obstruction. Further examination of the internal nasal cavity can be conducted using a headlight and thudicum nasal speculum to identify abnormalities such as deviated nasal septum, septal perforation, enlarged turbinates or nasal polyps. This should be followed by simple examination of the oral cavity and oropharynx, starting with observation of the state of dentition as this may determine the suitability of the patient to use a mandibular advancement device. Other features to be noted should include limitation of mouth opening, laxity of soft palate, size of palatine tonsils, the length of uvula and the general crowdedness of the oropharynx. The Mallampati palate position[12] and Friedman tongue position[13] may also be used for further evaluation of the upper airway obstruction and may provide an indication as to the likelihood of success of certain surgical interventions.

More detailed examination of the nose and the pharynx should be carried out using a flexible, fibre-optic endoscope assessing the nasopharynx, oropharynx and the hypopharynx. The patient could simulate the snoring[14] whist the endoscope is in position and could also perform the Mullers[15] manoeuvre, which essentially is the reversed Valsava manoeuvre. Although these may provide an insight in to the site and severity of upper airway obstruction, one must bear in mind that this 'awake' assessment in the patient may not truly reflect the upper airway dynamics during sleep as the muscle tone would vary greatly. Furthermore, some patients do find these manoeuvres difficult to perform and there may be a great deal of subjectivity in its interpretation.

INVESTIGATIONS

Before embarking on any treatment, it is important to perform some investigations. For instance, blood tests to exclude anaemia and hypothyroidism should be carried out to exclude other causes of tiredness. A sleep study should be performed in individuals where history is suggestive of OSA, to determine the severity of the problem. Other investigations to assess upper airway obstruction include imaging, acoustic analysis, sleep nasendoscopy (SNE) and use of pressure transducers.[16]

Imaging

Although not routinely utilized, imaging can be useful under certain circumstances. For example, in patients being considered for radical surgery like maxillo-mandibular advancement, cephalometry provides vital information about upper airway dimensions.[17] Disadvantages of this kind of imaging include the fact that it can only be performed whilst the patient is awake, the exposure to radiation and the cost. It only provides two-dimensional information and may also not be widely available. More detailed and sophisticated data can be obtained by using computed tomography (CT) scanning or magnetic resonance imaging (MRI), allowing objective volumetric dimensions of the upper airway to be calculated.[18,19] These are both expensive, and CT scans also involve radiation. The MRI scans are very useful in evaluating the soft tissue aspect of the upper airway. Using these routinely during sleep would not be cost-effective or practical.

Acoustic analysis

In general, this form of evaluation is considered to be entirely safe as it is non-invasive, does not involve radiation, is relatively cheap and can be utilized during natural sleep over multiple nights. It can be conducted simultaneously with a hospital-based polysomnography or at home with an ambulatory sleep study. By using the sound frequency spectrum, acoustic analysis can potentially distinguish between primary snoring and OSA.[20] Attempts have been made to correlate snoring sound frequency with different anatomical levels of upper airway obstruction, and comparison of this technique has been made to SNE.[21] This was found to be difficult, particularly with multilevel involvement in most patients. The sensitivity and specificity of acoustic analysis has often been questioned and its role in selecting different treatment modalities is slightly limited.[22]

Sleep nasendoscopy

SNE, which is more popularly known as drug-induced sedation endoscopy (DISE) in the rest of Europe, was pioneered at the Royal National Throat, Nose and Ear Hospital in London.[23] Work from this institute, including an audit study of 2485 procedures, has demonstrated that SNE correlates well with AHI and mean oxygen desaturation values.[24] The beauty of this technique lies in the fact that it allows a three-dimensional visualization of the upper airway dynamics during sleep, albeit drug induced. It has to be appreciated that the muscle tone of the upper airway is different when the patient is fully awake compared to when they are asleep and therefore the assessment of the anatomy during sleep should prove to be useful. It has been demonstrated that SNE is useful in predicting treatment success in snorers using mandibular advancement devices.[25–27] Similarly, SNE has allowed site specific selection in surgical patients and improved surgical outcomes in patients undergoing laser palatoplasty with or without tonsillectomy, as well as with implanted upper airway stimulation therapy for OSA.[28–31]

This assessment should be carried out in an operating theatre setting with the help of an anaesthetist and adequate cardiovascular and respiratory monitoring. The sedative agents used are midazolam or propofol, or a combination of the two, where midazolam effectively induces sleep while propofol, with its rapid onset of action and recovery, is useful in the fine tuning of sleep.[24]

Advocates of SNE find it to be a useful evaluation technique but numerous controversies and debates have arisen. First and foremost, drug-induced sleep is different from natural physiological sleep as the drugs used may cause exaggerated muscle relaxation. However, one could argue that this impact of the sedation drug would be similar on the different segments of the pharynx; thus, it would theoretically allow us to compare the proportionate obstruction caused at each anatomical level in a similar manner that may exist in natural physiological sleep. Furthermore, criticisms were made by Marais,[32] who claimed that, when comparing snorers and non-snorers during SNE, snoring was not reproduced in some of the snorers and snoring could be produced in the non-snoring group, and thus concluded that SNE was not an appropriate technique. This was challenged by Berry et al,[33] who elegantly demonstrated in their study using target controlled infusion of propofol during SNE that all their snorers and non-snorers responded as expected, thus validating and advocating SNE. Questions and concerns raised about test-retest reliability and of inter-observer variation during SNE have been adequately addressed by various studies.[34–36] Another concern that has been expressed is about the depth or level of sedation at which the upper airway should be evaluated. If the patient is assessed too early, the muscle relaxation effect of the sedation drug may be over-emphasized; and if the patient is assessed whilst too deep then important obstructive episodes during lighter sleep may be missed. This has been clarified by studies that have utilized bispectral index monitoring during SNE.[37,38] This neurophysiological monitoring device continually analyzes a patient's electroencephalogram during sedation or general anaesthesia and gives an indication of depth of sedation.

A recent study using digital videostroboscopy during SNE[39] has shown that whilst assessing the upper airway during sedation, stroboscopic evaluation may help further understanding of the mechanisms of airway obstruction, particularly in those who have failed surgical treatment.

It is important to accurately document the findings of the upper airway evaluation during SNE. At present there are various classifications[40–42] and although there is some overlap and commonality amongst these, ideally we need a uniform grading system. To date the only technique that allows evaluation of the upper airway during sleep in conjunction with dynamic visualization is SNE and the use of this technique has further emphasized the differences between awake and asleep assessment.[43, 44]

Pressure transducers

Various devices that can measure pressure changes in the different segments of the upper airway have been described. This allows pressure recording in various anatomical sites of the upper airway during obstructive episodes. It is now common practice to use a multichannel pressure catheter[45, 46] to record pressures at different anatomical levels of the upper aerodigestive tract ranging from the nasopharynx to the oesophagus, where usually the reference transducer is positioned. These have been used to ascertain the level of obstruction before performing the appropriate surgical procedure. One of the more recent devices, known as Apnea-Graph AG200 (MRA, Medical UK), seems quite promising in that it is able to perform the dual function of providing severity of OSA as well as some idea of the site of anatomical obstruction simultaneously,[47, 48] during natural physiological sleep as well as during sedation endoscopy. It relies on measuring pressure and airflow simultaneously at different levels in the pharynx. It has the ability to store and analyze the cardio-respiratory data of a patient with simultaneous recording of two different sites in the upper airway using a micro-pressure and temperature transducer catheter. Problems that may potentially be encountered with this device include difficulty in tolerating the catheter for the whole night and the possibility of some movement of the various transducers during different phases of respiration and, therefore, the site of obstruction may not be very accurately detected. Furthermore, the transducers are in a fixed position on the catheter and do not consider the morphological variation in the distances between different anatomical landmarks in individual patients.

NON-SURGICAL TREATMENT OF SNORING AND OSA

Snoring patients with or without obstructive sleep apnoea (OSA) should be advised to try non-surgical measures before contemplating any surgical procedures. An advice leaflet on self-help suggestions could be prepared locally. Otherwise, patients are directed to a national association website to provide them with the advice and support that they need. In the UK, they are directed to the British Snoring & Sleep Apnoea Association website (http://www.britishsnoring.co.uk). These measures revolve around lifestyle changes or the use of devices to alleviate the snoring.

Lifestyle changes

- Dietary modification for weight loss is essential. Morbidly obese patients are advised to explore the option of bariatric surgery if they fail to reduce their weight with dietary measures. A recent study investigating the effect of weight loss surgery in 1728 patients showed significant improvement of all obstructive sleep apnoea symptoms compared to controls. The average reduction of BMI was 9.7 kg/m^2.[49]
- Avoiding alcohol before sleep helps by reducing the detrimental effect of alcohol on the muscle tone of the neck. A randomized control trial showed that the ingestion of alcohol was associated with a significant increase in the number of apnoeic events and oxygen desaturation.[50]
- Avoiding smoking.
- Positional therapy, avoiding the supine position using the tennis ball technique, helps a small group of patients as its associated discomfort reduces the patient's compliance.[51]
- Regular exercise improves the tone of the muscles of the neck and also helps the patient to lose weight.

Devices

MANDIBULAR ADVANCEMENT SPLINTS

Mandibular advancement splints (MAS) produce forward displacement of the mandible, thus bringing the tongue base anteriorly, increasing the dimensions of the upper airway. There are a number of devices available in the market. The maximal degree of mandibular protrusion should be assessed, and then the MAS should be designed to maintain the mandible between 50% and 75% of the maximal protrusion. For simple snorers, MAS was found to be better than placebo in the subjective improvement of snoring.[52] For sleep apnoea, a randomized controlled crossover study showed significant reduction of the apnoea hypopnoea index using the MAS when compared to a control palatal plate.[53] A recent systematic analysis showed that the improvement of the OSA with MAS was observed in an average of 52%.[54]

The reported side effects of MAS include excess salivation, xerostomia, temporomandibular joint (TMJ) pain and bite change. The overall compliance is around 50–75%.[52, 55]

CONTINUOUS POSITIVE AIRWAY PRESSURE (CPAP)

CPAP is the treatment of choice for OSA. It is also recommended for upper UARS, which is referred to as sleepy snorers. It acts as pneumatic stent to prevent upper airway collapse throughout the different phases of sleep breathing. The CPAP machines could be either fixed pressure or autotitrating, according to the flow generator delivering the pressure through air tubing to a nasal mask, nasal prongs or a face mask worn by the patient. The average pressure required is 5–10 cm H_2O. The night to night pressure required overnight was found to be variable,

therefore the autotitrating CPAP would be a better option for the patients.[56]

The average use of CPAP in compliant patients ranges from 2–6 hours per night. A recent study showed that the longer the use of CPAP per night, the better the improvement of daytime somnolence and the functional status of the patients.[57]

Side effects include nasal congestion, rhinosinusitis, nasal bridge and facial irritation, and nose bleeds. Poor compliance is usually related to the discomfort of the device or the noise of the machine.

SURGICAL TREATMENT FOR SNORING AND OSA

Surgery to correct or improve upper airway obstruction may involve minimally invasive soft tissue surgery with no gross change in the anatomical structure such as interstitial radiofrequency thermotherapy or, at the other extreme, may involve radical skeletal framework surgery such as maxilla-mandibular advancement.

Nasal surgery

Patients who present with significant nasal obstruction secondary to deviated septum, nasal polyps or nasal valve collapse in addition to the snoring, should be offered the appropriate nasal surgery. There is strong evidence in the literature that nasal surgery would improve the nasal airway but the impact on snoring would be minimal. A prospective study of 40 patients showed objective improvement of the nasal airway using rhinomanometry without any improvement of the snoring time, snoring intensity, nocturnal breathing or sleep architecture.[58] Another recent controlled study revealed no change in the polysomnographic parameters after nasal surgery, although the nasal airway was significantly improved.[59]

The rationale in performing nasal surgery in patients with snoring with or without OSA is to improve their nasal airways and to provide them with a better response and compliance with CPAP. Friedman et al. investigated the result of nasal surgery alone on OSA and showed no significant impact on the respiratory disturbance index (RDI) or lowest oxygen saturation levels, but CPAP levels required to correct OSA were reduced.[60]

Uvulopalatopharyngoplasty

The classic uvulopalatopharyngoplasty (UPPP) described by Fujita et al. in 1981[61] involves the excision of the uvula, the removal of 1–2 cm of the oral palatal mucosa in curvilinear fashion along the anterior pillars, followed by excision of the excess length of the soft palate. Then the nasopharyngeal mucosa is pulled anteriorly and laterally to widen the nasopharyngeal airway. Simmons et al.[62] described a modification that was adopted in the UK involving the excision of the tonsils, the uvula, half of the anterior and posterior pillars, and full thickness of the lower part of the soft palate. The soft palate was palpated and the incision was made posterior to the fold of the levator sling then followed by suturing of the anterior and posterior pillars in continuation with the inferior margin of the remaining soft palate. A number of modifications introducing different types of local flaps[63–69] were described to maximize the size of the oropharyngeal airway, in an attempt to improve the success rate and to reduce the incidence of post-operative complications. Using an outcome measure of a reduction of snoring level by 50%, the early post-operative success rate was 76%; however, the long-term success rate was only 45% with a low overall satisfaction.[70] In addition to this low success rate, a prospective multicentre study showed 1.5% incidence of serious non-fatal complications and a mortality rate of 0.2%.[71] Post-operative pain is a constant complaint after UPPP and patients should be warned about it.[72] Exacerbation of sleep apnoea and respiratory obstruction have been reported in the perioperative period as a result of the use of sedatives, muscle relaxants or post-operative pain management.[73] This early post-operative airway compromise might also be related to the resultant oedema of the tissues and it was noted to be directly proportional to the severity of sleep apnoea.[74] The most common late complication following UPPP is velopharyngeal insufficiency (28.5%),[75] which is related to scarring and excessive palatal resection.[76] Other complications include bleeding (0–6%), dry throat (10%), infection (0–10%), and swallowing problems (0–9%).[77, 78]

Potentially, UPPP might compromise the future use of nasal CPAP therapy because of the loss of the soft palate seal resulting in excessive mouth air leak. Mortimore et al. reported that patients after UPPP significantly tolerated less pressure and their compliance was poorer than sleep apnoea patients without UPPP.[79] The face mask CPAP has provided a solution to this issue but its compliance is worse than nasal CPAP.

Because of these associated complications, alternative approaches have been introduced.

Laser-assisted uvulopalatoplasty

Laser-assisted uvulopalatoplasty (LAUP) refers to a number of different techniques involving the use of the laser to the soft palate for the treatment of snoring. The first technique was described by Kamami in 1990, using a CO_2 laser to create vertical trenches in the soft palate (up to 2 cm) on either side of the uvula followed by partial vaporization of the uvula.[80] Numerous modifications of this technique were described using it, in single or multistage fashion, to stiffen the soft palate.[81–84] The second technique was introduced by Ellis in 1993, using an Nd-YAG laser to remove a 1.5 cm wide central longitudinal strip of mucosa from the whole length of the soft palate followed by excision of the uvula at its base.[85] Other modifications were described, extending the excised part of the mucosa, with or without using flaps of the palate, performed under local or general anaesthesia.[86–88] The aim of LAUP is to invite scarring to the soft palate, making it stiffer to minimize snoring due to palatal flutter.

The post-operative pain is worse than UPPP, with the peak reached on the 3rd post-operative day and it takes up to 15 days to resolve completely. The short-term success rate is 79%, dropping to 55% in the long term.[89–91] Other complications reported were haemorrhage (2.12%), local fungal infection (0.53%), temporary palatal incompetence (0.53%), temporary loss of taste (0.27%)[90] and globus type symptoms.[92] It has no significant impact on smell and taste.[93]

In a recent systematic review,[94] only two randomized controlled trials[95, 96] were found, with no significant difference between LAUP and controls in the treatment of snoring with or without mild sleep-related disorders. It was reported that some simple snorers developed mild OSA following LAUP. This might be related to increased palatal fibrosis, contraction of the velopharyngeal space and reduction of the space between the posterior pillars.[97]

Radiofrequency tissue volume reduction/thermal ablation (CAUP)

This technique employs the use of low frequency radio waves, delivered into the submucosal tissue with the tip of a wand, to create a channel of charged ions that heats the tissues, causing denaturation of the proteins and cell lysis at low temperatures (60–90°C). This destroys specific areas of tissue with minimal collateral damage to tissues, inviting scarring to the muscle layer, reducing its volume and making it stiffer.[72, 98, 99] Three radiofrequency devices are available: the Somnus unit;[99] the Celon device;[100] and the coblator unit.[101]

The main advantages of this technique are that it can be carried out under local anaesthesia and used at multiple levels. For the soft palate, using the somnus device, three channels are made in each side of the soft palate in addition to two lesions in the paramedian position with the entry point just distal to the junction between the hard and soft palate. However, with the Celon device, which uses bipolar technology, more than three applications to the soft palate can be made. A special technique called coblation assisted upper airway procedure (CAUP) was described by Tvinnereim et al.[46] This consisted of making a lateral palatal incision on each side, ablating three upward channels on each side of the midline (fan-shaped) into the soft palate, performing a partial uvulectomy with two upward channels in the uvula and finally channelling of the anterior and posterior pillars and the tonsils if they are present. Multilevel therapy of the palate, base of the tongue and tonsils was described, with a 33% improvement in OSA patients.[101] The long-term success rate of radiofrequency treatment to the palate was found to be 37%.[102] A recent review reported better visualization of the tongue base for the application of the probe by applying simultaneous pressure over the mylohyoid and the thyroid cartilage.[103] It also emphasized the point that general anaesthesia may be the preferred option if multilevel application of radiofrequency is needed to treat the soft palate and the tongue base simultaneously.

In general, radiofrequency treatment is associated with less pain than UPPP or LAUP. Complications reported after radiofrequency tissue ablation of the soft palate included haemorrhage, infections and velopharyngeal fistula in single cases.[72, 103, 104] For radiofrequency ablation of the base of the tongue, studies showed incidence of infections or tongue abscesses in 0–8% of patients, with few cases of temporary tongue base neuralgias.[105, 106] Single cases of mouth floor oedema and severe tongue swelling, and a case of pseudo-aneurysm of the lingual artery and heavy bleeding 14 days after surgery have also been reported.[105, 106]

Transoral robotic surgery for tongue base

A recent development in the surgical management of OSA is the use of da Vinci robot, allowing transoral robotic surgery (TORS). This is being utilized for patients with severe OSA who have failed CPAP treatment and persistent hypopharyngeal obstruction following experiences in tongue base malignancy.[107]

A minimally invasive telerobotic system allows excellent 3D visualization, immaculate precision and absence of tremor. This improved access allows oropharangeal enlargement anteriorly through tongue base reduction and treatment of inward inspiratory collapse of a floppy epiglottis, aryetenoids and aryepiglottic folds. Vicini et al.[108] present their preliminary outcome data at 3 years, demonstrating a polysomnogram success rate (post-op apnoea hypopnea index < 15) of approximately 80%. No emergency post-operative interventions were required and good functional results in pain, swallowing and quality of life were displayed.

The surgery was, however supplemented with multiple other procedures in the case series, including septoplasty, UPPP, supraglottoplasty, turbinate reduction and ethmoidectomy. Similarly, another case series[109] presents favourable outcomes using a transoral robotic technique in combination with palatal surgery. The potential confounding factors of these additional procedures presents us with a difficulty in interpretation of these results, yet additionally places further value on the evolving concept of multilevel surgery when the outcomes are reviewed.[110] The peri-operative management for these patients varies between centres but increasing experience in the technique and knowledge of the potential complications has led to a drive away from a prophylactic or 'covering' tracheostomy as standard part of the patient pathway.

Lin et al.[111] demonstrate the use of a TORS technique in isolation for tongue base obstruction, excluding patients who received additional forms of upper airway alteration. This case series is small, with only 12 patients, yet a statistically significant reduction in AHI is demonstrated from this preliminary data.

A robotic surgical approach to hypopharangeal obstruction is likely to be applicable to a small subset of patients with severe obstructive sleep apnoea. Present case series analysis suggests that, for adequately selected individuals, a robotic approach may yet prove an appropriate treatment modality within specialist centres with the requisite equipment and experience.

Less performed procedures

CAUTERY ASSISTED PALATAL STIFFENING OPERATION

Cautery assisted palatal stiffening operation (CAPSO) involves the use of an electrocautery needle to remove a 2 cm inverted 'U' area of mucosa from the soft palate, in addition to the mucosa and part of the uvula. It is left to heal by secondary intention to stiffen the soft palate.[112] There are no controlled studies to evaluate this technique, but the few studies there are suggest a success rate similar to UPPP, with minimal complications.[113]

INJECTION SNOREPLASTY

The injection of 2 ml of a sclerosing agent in the midline of the soft palate above the base of the uvula was reported to invite enough scarring to make it stiffer. In the literature, 3% sodium tetradecyl sulphate, 50% ethanol and doxycycline were used in selected patients. The procedure is performed in the outpatient setting under local anaesthesia and can be repeated within 2 years if it does not improve the snoring. Although two cases of palatal fistulae were reported, they healed spontaneously and no other complications were noted.[114]

PILLAR IMPLANTS

In this technique the palatal stiffening is achieved by the implantation of woven Dacron mesh into pockets dissected in the soft palate.[115] A systematic review of four studies showed subjective improvement in VAS scores up to 53%, but no significant difference was reached in any objective snoring indices. It is associated with mild pain with a rate of extrusions of 0–11%.[116]

MANDIBULAR AND MAXILLARY SURGERY

A number of procedures were described in the literature aimed at dilating the hypopharynageal airway, including genioglossus advancement, tongue base suspension suture, hyoid suspension, maxillomandibular advancement and laser midline glossectomy. Most of the reports describing these procedures are pilot studies with no standardized comparison of other techniques used in the treatment of OSA. The reported success rate of some of these procedures approaches 60% in the short term. These procedures are associated with relatively high complication rates, such as swallowing problems, taste change, tongue oedema, tooth numbness and mandibular fractures. The midline laser glossectomy was associated with a high incidence of post-operative bleeding.[117]

TRACHEOSTOMY

Surprisingly enough, tracheostomy was the first surgical intervention in patients with OSA even before the disease was fully recognized. In 1980, Guilleminault et al. reported the long-term results after tracheostomy as a single intervention for OSA with resolution of the clinical symptoms and return to full activity.[118] However, the advent of the above mentioned surgical interventions have meant that tracheostomy is rarely indicated for the management of OSA. The American Academy of Sleep Medicine (AASM) has published a recent update on practice parameters for the management of OSA, emphasizing that tracheostomy should be considered only when other options do not exist, have failed or are refused, or when this operation is deemed necessary by clinical urgency.[119]

HYPOGLOSSAL NERVE STIMULATION

Experimental research in both humans and animals has demonstrated an increase in pharyngeal neuromuscular activity during sleep in obstructive sleep apnoea patients but at an insufficient level to overcome airway collapse. As such, there has been a focus on selective stimulation of upper airway dilator muscles (e.g. genioglossus) to improve airway patency without arousing patients from sleep. An implantable neurostimulator to synchronize hypoglossal nerve stimulation with inspiration has shown early promise in a single arm feasibility study.[120, 121] Twenty-one patients were recruited with moderate to severe OSA who had failed to tolerate CPAP. A significant decrease in OSA symptomology and in-laboratory polysomnography was established at 6 months post-implantation. Two device-related 'serious' adverse events occurred in this cohort, necessitating removal or replacement. Long-term safety and efficacy of this treatment warrants further clinical evaluation but it remains a treatment modality with high expectations for future benefit given the technological advances in this area.

CONCLUSION

Patients with sleep-related breathing disorders are best dealt with using a multidisciplinary approach. Lifestyle changes, appliances and surgical intervention are all treatment modalities that are available for these patients and a combination of these treatment options may be required to adequately resolve their problem. Thorough assessment and careful patient selection, particularly for surgical treatment, is essential for a successful outcome.

KEY POINTS

- Treatment of sleep-related breathing disorders require a multidisciplinary approach.
- Lifestyle changes and appliances should be utilized before surgery is considered.
- Careful patient selection for surgery is necessary.
- SNE is useful in tailoring site-specific treatment.
- Multilevel problems are very commonly seen therefore multilevel surgery may be required.
- It may be necessary to use appliances in conjunction with surgery.

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CHAPTER 76

LARYNGOTRACHEAL STENOSIS IN ADULTS

Guri S. Sandhu and Reza Nouraei

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SEARCH STRATEGY

Data in this chapter may be updated by a PubMed search using the keywords: stenosis, subglottis, laryngotracheal, reconstruction, resection, tracheal, granulomatosis, vasculitis, sarcoid, bilateral, cord and stents.

INTRODUCTION

The upper aerodigestive tract, larynx, trachea and bronchi form the conduit between the external environment and the lungs to facilitate gas exchange. The larynx acts to protect the airway from aspiration during swallowing. It is the primary organ for phonation but also provides important sensory feedback and movements that are critical to the control of ventilation. The narrowest site of the adult airway is the glottis, whereas in infants it is the subglottis.

In the middle of the last century, the discovery of antibiotics and the ability to ventilate patients for prolonged periods meant that infections were no longer the principle cause of laryngotracheal stenosis (LTS). A period of ventilation on the intensive care unit (ICU) is now the most common cause of laryngotracheal injury and stenosis. Approximately 50% in our series of adult airway stenosis is post-intubation (**Table 76.1**, authors' series) and this figure is higher in children.[1] Risk factors include duration of ventilation, sizing of ventilation tubes, excessive cuff pressures, irritation from orogastric secretions, infections, immune disturbance and the patient's response to injury and healing biology.

Abnormal narrowing of the laryngotracheal complex causes breathlessness, especially during physical activity, and retention of pulmonary secretions may lead to lung infection or collapse. Laryngeal stenosis can also interfere with phonation and a dysfunctional larynx can impair swallowing safety. The exact physiology of dyspnoea is not known but the extra effort of breathing, tendency towards carbon dioxide retention and afferent signals from the respiratory tract must play a part.

TABLE 76.1 Aetiology of laryngotracheal stenosis in 600 consecutive referrals to the National Centre for Airway Reconstruction

50.3% Acquired laryngotracheal stenosis	• 34.3% subglottic stenosis • 16% tracheal stenosis
16.67% Bilateral vocal cord mobility impairment	(Nerve injury, scar/fixation, rheumatoid arthritis)
10.0% Wegener's granulomatosis	
8.67% Idiopathic subglottic stenosis	
5.70% Supraglottic stenosis	(2.7% sarcoid, 3.0% other)
2.33% Previous papillomatosis treatment	
2.33% Glottic web	
1.33% Tracheomalacia	(0.67% relapsing polychondritis)
1.17% Vascular lesion	
0.83% Amyloidosis	
0.67% Subglottic stenosis congenital	

Although the incidence of post-intubation LTS is unknown, one series reports significant airway injury in 47% of patients bronchoscoped at extubation.[2] Long-term airway compromise has been estimated at between 1% and 4%.[3–6] This means that the initial fibro-inflammatory injury appears to resolve in the majority of cases and only in some patients, through healing by fibrosis and wound contracture, does it lead to persistent airway narrowing. However, it is also possible in the absence of high quality follow-up data that some patients live with dyspnoea after the ICU and their LTS is never diagnosed.

PATHOPHYSIOLOGY OF LARYNGOTRACHEAL STENOSIS

In laminar airflow, airway resistance is dictated by the diameter of the airway and by the density of the inspired gas (Poiseuille's law):

$$R = \frac{8nl}{\pi r^4}$$

where:

- R = resistance
- n = viscosity
- l = length
- r = radius.

The resistance to airflow, by a stenotic segment of airway, is proportional to its length but inversely proportional to the fourth power of its radius. Turbulence, although difficult to calculate, is also inversely proportional to the airway diameter and will further add to resistance to airflow.

During inspiration, the intrathoracic airways expand along with the expanding lungs. However, the extrathoracic trachea will have a reduced lumen during inspiration because the intraluminal pressure is lower than atmospheric. The reverse happens during expiration. A variable obstruction of the airway also changes size with breathing. Hence, an extrathoracic variable tracheal stenosis will limit inspiration whereas an intrathoracic variable lesion will limit expiration. A fixed obstruction, whether intrathoracic or extrathoracic, will limit peak airflow on inspiration and expiration in equal proportions and produce a characteristic flow volume loop (**Figure 76.1**).

DIAGNOSIS

Diagnosis of LTS starts with the history. Previous prolonged ventilation, duration of shortness of breath and coexisting medical problems such as vasculitis or sarcoidosis are relevant. Symptoms of dyspnoea, voice changes and chronic cough are common but questions should also be directed to determine impairment of swallowing function and history of laryngopharyngeal reflux.[7] Exertional dyspnoea is the main symptom and patients compensate by reducing their physical activity. Patients can compensate over time for chronic progressive airway stenosis whereas the same level of stenosis occurring acutely may result in significant disability and even death. Chronic airway obstruction is sometimes misdiagnosed as asthma or chronic obstructive pulmonary disease.

Examination should document the severity of stridor, chest recession, body morphology (body mass index) and neck scars. Fibre-optic nasal endoscopy will help assess vocal cord mobility, evidence of laryngopharyngeal reflux, pooling of secretions in the hypopharynx and the degree of stenosis if it lies within the larynx or cervical trachea. If a tracheostomy is in place, the lower airway can also be assessed with the same flexible endoscope and sometimes a retrograde examination of the subglottis is also possible if the patient will tolerate temporary removal of the tracheostomy tube.

Investigations include imaging using high definition tomography (CT) but care should be taken when interpreting these scans. As the scans reconstruct the image from 'cuts' taken at intervals, if these cuts miss the apex of the stenosis than they will underestimate or even miss the problem. Conversely if there are secretions over the stenosis then overestimation of stenosis may occur. Respiratory function testing is essential to determine the severity of airway compromise but also to monitor the response to treatment. The minimal requirement is spirometry and flow

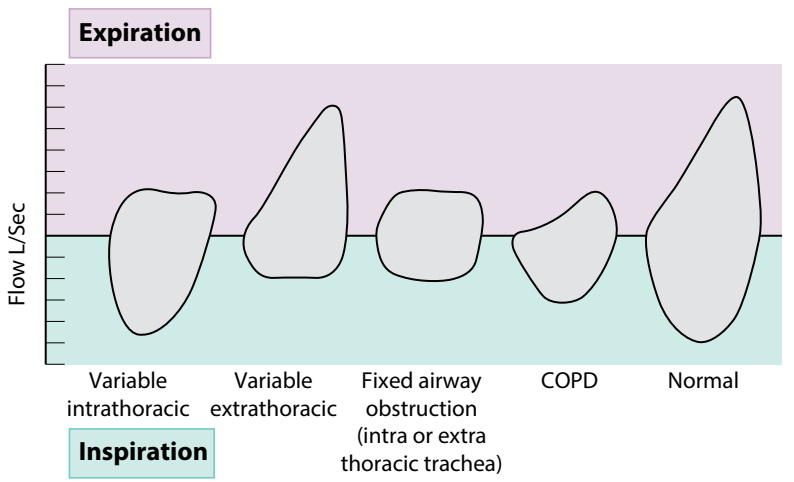

Figure 76.1 Characteristic flow volume loops. (Left to right): soft intrathoracic stenosis, soft extrathoracic stenosis, fixed stenosis anywhere in larynx or trachea, chronic obstructive pulmonary disease and a 'normal' flow volume loop.

volume loops and ideally cardiopulmonary exercise testing. If there is any evidence of disordered swallowing, then fibre-optic endoscopic evaluation of swallowing (FEES) or videofluoroscopy is essential. There are poor outcomes reported in patients with even minor aspiration, following airway reconstruction.[8] Although the majority of our patients are prescribed antireflux advice and therapy (once or twice daily proton pump inhibitor with an alginate suspension after the evening meal), it is still of value to investigate for laryngopharyngeal reflux in the symptomatic patient in case antireflux surgery is indicated.

Patients with airway stenosis must be managed by a multidisciplinary team that includes an ENT and thoracic surgeon, pulmonologist, anaesthetist, radiologist, pathologist and speech and swallowing therapist as well as a dietician. Bariatric services should also be available as there is an increase in the resting metabolic rate in obesity as well as decreased respiratory performance and exercise tolerance. Outcomes of airway surgery are also poorer in the overweight patient.[8]

INTRA-OPERATIVE ASSESSMENT OF POST-INTUBATION LARYNGOTRACHEAL STENOSIS

Paediatric LTS is a well-researched area of otolaryngology. Paediatric LTS nearly always involves the subglottis[9] and prolonged endotracheal intubation is by far the most common cause. Treatment strategies include airway augmentation with rib grafts as well as tracheal and cricotracheal resections. The lesional anatomy and pathology behind paediatric LTS differs greatly from the adult group. Adult LTS has been poorly researched and the surgical options include tracheostomy, tracheal resection or cricotracheal resection.[10] Some surgeons still use primary cartilage grafts to augment the adult airway. There appears to be poor appreciation of the fact that there is a high incidence of ischaemic necrosis of primary rib graft in adult patients.[11] Furthermore, the quality and quantity of rib cartilage that can be harvested diminishes with age.

The definitive airway assessment is airway endoscopy. Endoscopic airway assessment is performed by respiratory physicians, thoracic surgeons and otolaryngologists. Pulmonologists and thoracic surgeons are usually trained to use both flexible and rigid bronchoscopes. Flexible bronchoscopy is most commonly performed in the spontaneous breathing and sedated patient who has had topical anaesthetic applied to the upper aerodigestive tract. This technique allows assessment of the dynamic airway, the trachea and bronchi with the ability to perform the full spectrum of interventions. However, with a flexible bronchoscope placed through a narrow stenosis, the patient's airway can become obstructed. Attempted airway dilatation also leads to temporary airway obstruction. Use of the rigid ventilating bronchoscope requires the patient to be paralyzed and ventilation maintained by a face mask, laryngeal mask or endotracheal tube until the bronchoscope is inserted. For assessment of the airway beyond an area of stenosis, the rigid bronchoscope may need to be forced through the stenosis. This has the effect of dilating the stenosis, but also causes stripping of the mucosa. Neither flexible nor rigid bronchoscopy allows prolonged access or endoscopic surgery on the larynx or subglottis. The otolaryngologist is able to utilize suspension microlaryngoscopy, with supraglottic high frequency jet ventilation, in a patient receiving total intravenous general anaesthesia. The microscope provides binocular vision (hence depth of field), better illumination, two hands free for surgery and use of the carbon dioxide laser using a line-of-sight technique. The laryngoscope also allows the use of rigid and flexible endoscopes, fibre lasers, pulmonary balloon dilators, microdebriders and stents. In the event that the patient's oxygen saturations 'dip' an endotracheal tube can be passed via the larynx to achieve positive pressure ventilation. The endotracheal tube is removed to allow completion of airway surgery.

It is important at endoscopy to assess vocal cord mobility and map the stenotic segment. The tip of the endoscope is placed at the lower end of the stenosis and a mark is placed on it at the level of the mouth of the laryngoscope. The endoscope is withdrawn so that its tip lies at the top of the stenosis and again so that its tip lies at the level of the glottis. Each of these points is marked and, with the use of a ruler, the length of the stenosis and its distance from the glottis can be determined. There are techniques for accurately calculating the size of the airway at the level of the stenosis;[12] however, for most purposes the Myer–Cotton grading system[13] allows stratification of airway stenoses to plan treatment (**Figure 76.2**).

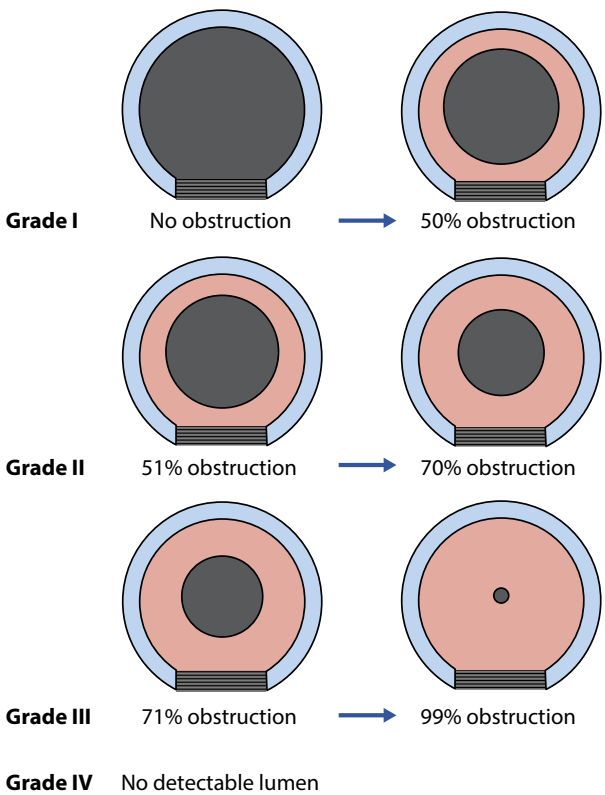

Figure 76.2 Myer-Cotton grading system for subglottic stenosis.

Although the first endoscopy is a staging procedure, some form of surgery is usually possible. Through a combination of imaging (CT) and endoscopy, a decision needs to be made as to whether there is significant damage to the cartilaginous support of the airway at the site of the stenosis. If this is the case then an endoscopic approach, including stenting, will only bring temporary relief of symptoms and an open surgical approach, such as a tracheal, or cricotracheal, resection or laryngotracheal reconstruction (LTR), needs to be considered.

SURGERY FOR POST-INTUBATION LARYNGOTRACHEAL STENOSIS

The majority of patients with post-intubation LTS start with an airway injury that is inflammatory or fibro-inflammatory (**Figure 76.3**).

These types of injury respond well to an endoscopic approach.[14] Using suspension laryngoscopy and supraglottic jet ventilation, up to three millilitres of Depo-Medrone (40 mg/ml) can be injected into the stenosis. Three to four radial cuts are then made into the stenosis using a carbon dioxide laser (8–10 watts) delivered through the operating microscope. The lesion is then dilated, using a pulmonary balloon dilator system, to the size of the adjacent normal airway.

More commonly, at presentation, the majority of cases of airway stenosis have already evolved into mature fibrotic lesion. Intralesional steroids are of limited value if the cartilaginous framework of the airway is intact; in this scenario, an endoscopic approach using radial laser cuts, balloon dilatation and topical mitomycin-C application may still be effective. The procedure usually needs to be repeated every 3–4 weeks until the airway has stabilized. By the third procedure, it is clear to the surgeon if the technique is going to work or whether an open procedure needs to be considered. Overall the endoscopic approach is successful in approximately two-thirds of cases of post-intubation LTS.[14] Failure occurs in cases of significant cartilage framework damage, stenosis length greater than 3 cm, obesity and in patients with swallowing impairment who tend to have persistent airway inflammation. The options are then tracheal (**Figure 76.4**) or cricotracheal resection. Unfortunately, in the adult patient, the maximum length of resection possible is 4–6 cm even with laryngeal and pulmonary release procedures.[15]

SURGERY FOR POST-TRACHEOSTOMY AIRWAY STENOSIS

A less common variant of post-ventilation tube related tracheal stenosis is seen in a small number of tracheostomy patients. This is probably due to over-resection or fracturing of anterior tracheal rings during insertion of a tracheostomy. At decannulation, there is scarring and contracture at the stoma site, which pulls in the lateral tracheal ring remnants leading to a 'lambda-shaped' stenotic deformity and airway compromise. The lesion usually extends over 1–2 tracheal rings with a normal proximal and distal trachea.[16] The trachealis is not involved and there is usually a small anterior bridge not contributing to the stenosis (**Figure 76.5**). Tracheal resection and anastomosis has been recommended for this condition,[17] but this is a major operation with associated morbidity and a small mortality rate.

The lesion can be treated using a CO_2 laser, delivering 8–10 W superpulsed, deployed through a micromanipulator attached to the microscope using a 'line-of-sight' technique. The proximal and distal trachea is used to guide the limits of the resection and the encroaching cartilage is vapourized. A pulmonary balloon dilator may be used to expand the airway. The mucosa over the trachealis and the apex of the Lambda must be preserved, as a circumferential injury with the laser will risk re-stenosis. The patient is usually discharged from hospital the following day with a short course of broad-spectrum antibiotic. The airway is

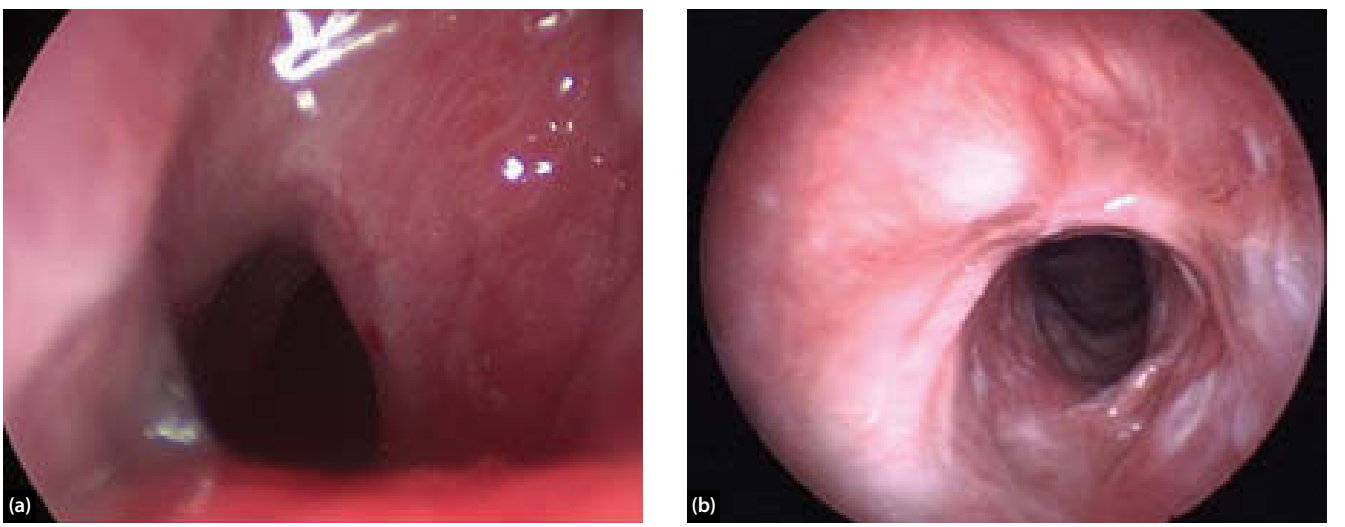

Figure 76.3 A very inflammatory airway stenosis as seen immediately post extubation (a). Stenosis has evolved to be more fibro-inflammatory **(b)**.

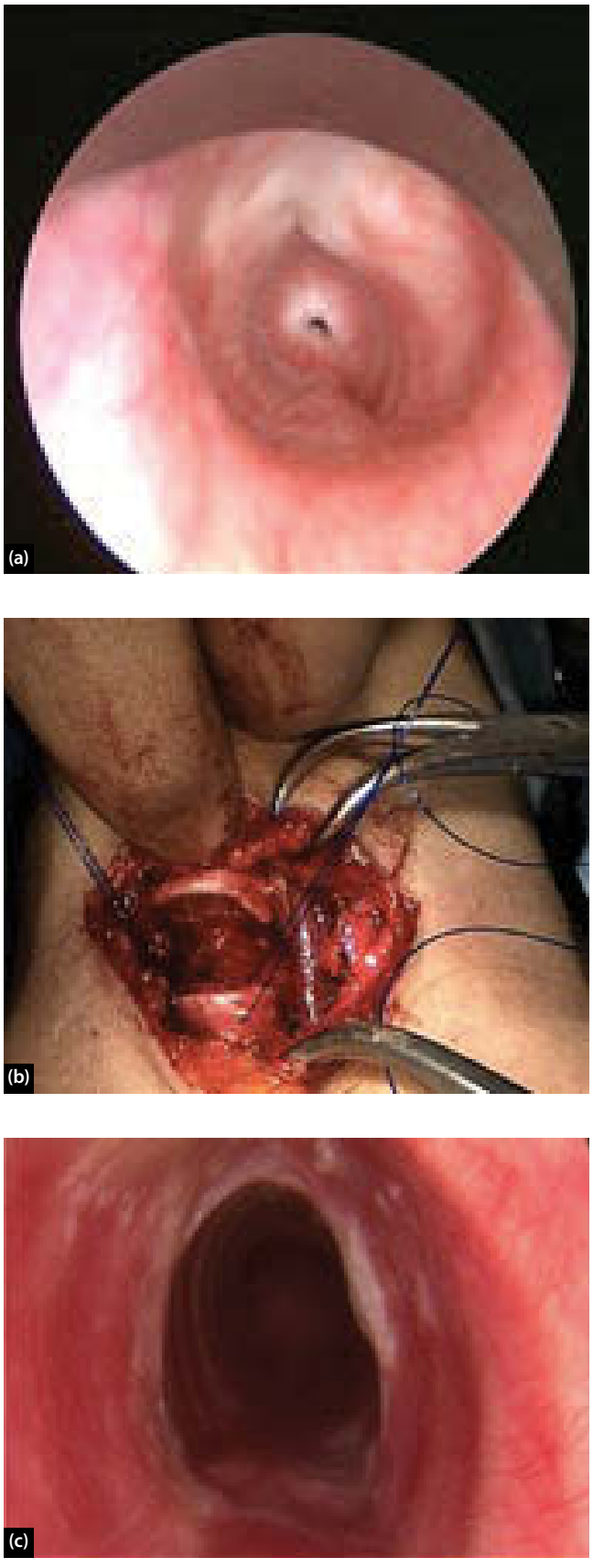

Figure 76.4 A cervical tracheal stenosis that is mature and fibrotic but also with loss of cartilaginous support (a). During a tracheal resection before anastomosis **(b)**. The same patient a few weeks after tracheal resection **(c)**.

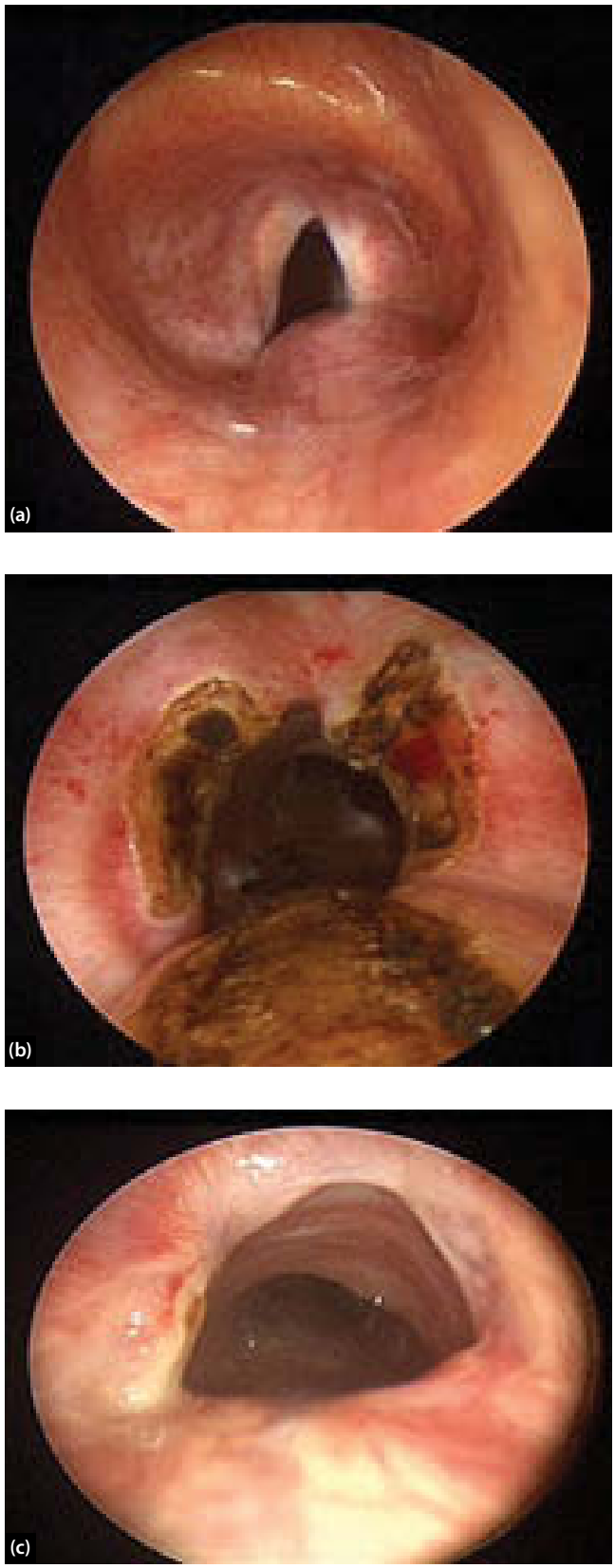

Figure 76.5 'Lambdoid' tracheal stenosis following decannulation (a). Intra-operative view after resection of tracheal cartilages with the CO_2 laser **(b)**. The bulging trachealis is managed with a gentle surface laser. Note bridges of normal mucosa between each site that is lasered. The same patient 3 months after surgery **(c)**.

reassessed, in theatres, at 3–4 weeks. Any residual cartilage or granulation is removed. It is unusual for a patient to require more than three endoscopic interventions for this condition. In these circumstances an open approach to tracheal resection should be considered.

TRACHEOBRONCHIAL STENTING

Charles Thomas Stent was a British dentist in the late 19th century. He developed dental impression material that was used as a template to support skin grafts for repair of oral trauma. Today, the term is used to describe devices for maintaining the patency of tubular structures, including the tracheo-bronchial tree. There is currently a variety of silicone and expandable metal stents for the airway (**Figure 76.6**). The metal stents can be uncovered, covered or partially covered (hybrid). Wire stents tend to be covered with polyurethane, although Teflon sheeting is used in some designs. The next generation of stents will be reabsorbable or bioengineered in other ways, negating the need for subsequent removal.

In benign and malignant disease, stents have been used to palliate the effects of large airway obstruction caused by extrinsic compression, endoluminal disease or loss of cartilaginous support. Indications in benign disease include long length stenoses, failed previous repair, patient comorbidities that restrict reconstructive surgery, or patient preference. Stents are also used temporarily following airway surgery.

Although patients with metal stents enjoy immediate palliation of symptomatic tracheal stenosis, metal stents are associated with a high incidence of obstruction with granulation.[18] They are also susceptible to metal fatigue and fracture over time. The authors recommend that uncovered or hybrid metal stents should only be used in a select group of patients with a short life expectancy.[19] If these stents are not removed within the first few weeks of deployment, they become a permanent fixture in the airway. They can fragment over time and cause granulation and bleeding. Silicone stents are easier to remove but have a higher incidence of migration unless sutured in place.[20] There is a high incidence of bacterial colonization of all stents, which can lead to granular tissue formation,[21, 22] the most common organisms being *Staphylococcus aureus* and *Pseudomonas aeruginosa*. It is widely accepted that wire stents have a higher incidence of granulation formation, especially at their ends. Some authors report that silicone stents have a higher incidence of mucus plugging than wire stents.[18] However, this experience largely relates to the use of stents in the bronchi. In the upper trachea, biofouling and mucus plugging is much greater in wire stents than in silicone stents. This may be due to the relative lower humidity in this area. The incidence of stent migration is widely reported as being higher in the subglottis than in the remainder of the tracheo-bronchial tree. The reason for this appears to be due to the fact that the subglottis is a fixed structure, without the expansion allowed by trachealis.

Usually silicone stents usually have to be placed under general anaesthesia, using a ventilating rigid bronchoscope. The authors use a technique of suspension laryngoscopy with supraglottic jet ventilation and placement of a silicone stent with rigid stent forceps. Visualization is assisted by a 0 degrees, 30 cm Hopkins optical endoscope, which is 4 mm in diameter or a flexible bronchoscope. Wire stents arrive preloaded in delivery devices and can be passed parallel to a flexible bronchoscope

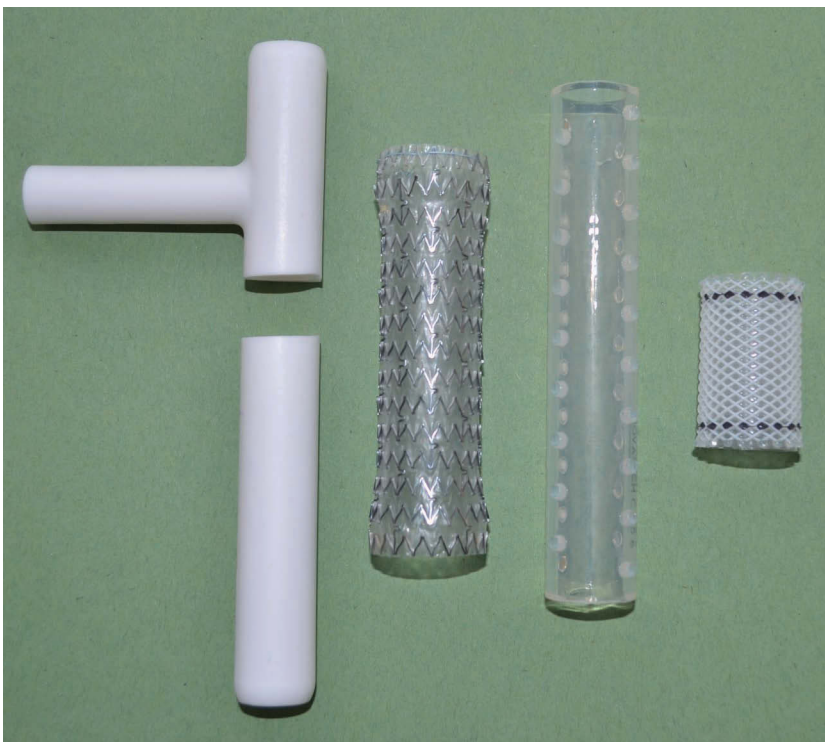

Figure 76.6 Left of image is a silicone stent fashioned from the vertical limb of a T-tube that has to be stitched into the airway. Centre left is a fully covered wire stent. Centre right is a silicone stent with external studs, which are to prevent migration. On the right is a covered mesh stent where the mesh is also made from a plastic polymer.

in a spontaneously breathing, sedated patient, or using fluoroscopic screening techniques. Wire stents can also be inserted under general anaesthesia. Stent removal is easiest using a general anaesthetic technique. This allows the use of rigid biopsy or grasping forceps to firmly grip the stent even if embedded in granulation. Uncovered wire stents that have been in place more than 3 months will usually require an open surgical approach for removal.[18]

Post-operatively, all patients with stents are prescribed daily saline nebulizers. Carbocysteine is added in those patients where there is evidence of mucus plugging.

IDIOPATHIC SUBGLOTTIC STENOSIS

Idiopathic subglottic stenosis (ISS) is a rare, slowly progressive, fibro-inflammatory process of unknown aetiology, leading to narrowing of the airway in the subglottis but also involving the first and second tracheal rings. Embryologically, there does not appear to be any developmental significance to this anatomical site, although it is an area of intense immune activity. ISS should strictly be called idiopathic LTS as it involves the proximal trachea and can extend up to the glottis.

It occurs predominantly in post-pubertal women, but has been reported in males,[23–26] and the majority of reported patients are Caucasians. The diagnosis is one of exclusion. The condition must follow the anatomical description above. There must be no history of intubation or tracheostomy in the last 2 years, no neck trauma or surgery and no neck radiotherapy. In each case, the antineutrophil cytoplasmic antibody (ANCA) and angiotensin converting enzyme (ACE) tests have to be repeated at intervals and prove negative. Tissue for histology is also sent at each surgical procedure to rule out other inflammatory conditions or a low-grade neoplasm.

The treatment approach varies from cricotracheal resection to repeated endoscopic procedures. The majority of patients can be managed with endoscopic airway surgery once or twice a year as described below. Examination under anaesthesia, using suspension laryngoscopy, supraglottic jet ventilation and rigid endoscopes, allows for the dimensions of the lesion to be determined. Up to 3 mL of methylprednisolone acetate is injected into the lesion using an appropriate needle. Three or four radial incisions are made into the lesion using the carbon dioxide laser set at 8–10 Watts. This laser is deployed through a micro-manipulator attached to the operating microscope. Following these radial cuts, the lesion is dilated using a pulmonary balloon dilatation system and the lesion is dilated to 15–16 mm (**Figure 76.7**). A deep tissue biopsy is taken at this stage using microcup forceps and haemostasis is achieved using topical adrenaline.

Aggressive laser ablation of the stenosis is not advised as this will risk more severe stenosis recurrence.

Cricotracheal resection has been used to treat this condition with reported good results[24] but others have failed to duplicate these outcomes.[26] ISS is primarily a mucosal disease that overlies healthy perichondrium and cartilage.[27] There is also concern that cricotracheal resection in a condition that predominantly affects females is likely to leave these patients with 'male-type' voices after the surgery.[28] Moreover, cricotracheal resection conceptually treats this condition as a benign neoplasm and, in our series, the disease often extends up to the glottis (**Figure 76.7**, left) and it is difficult to conceive how a resection could be performed within millimeters of the vocal folds without causing damage to this area.

With have described a different approach, which can be used to permanently treat all variations of this condition. A laryngofissure and posterior cricoid split is performed. The majority of the stenosed mucosa is removed and a piece of costal cartilage is placed as a 'spacer' to expand the posterior cricoid split (**Figures 76.8** and **76.9**).

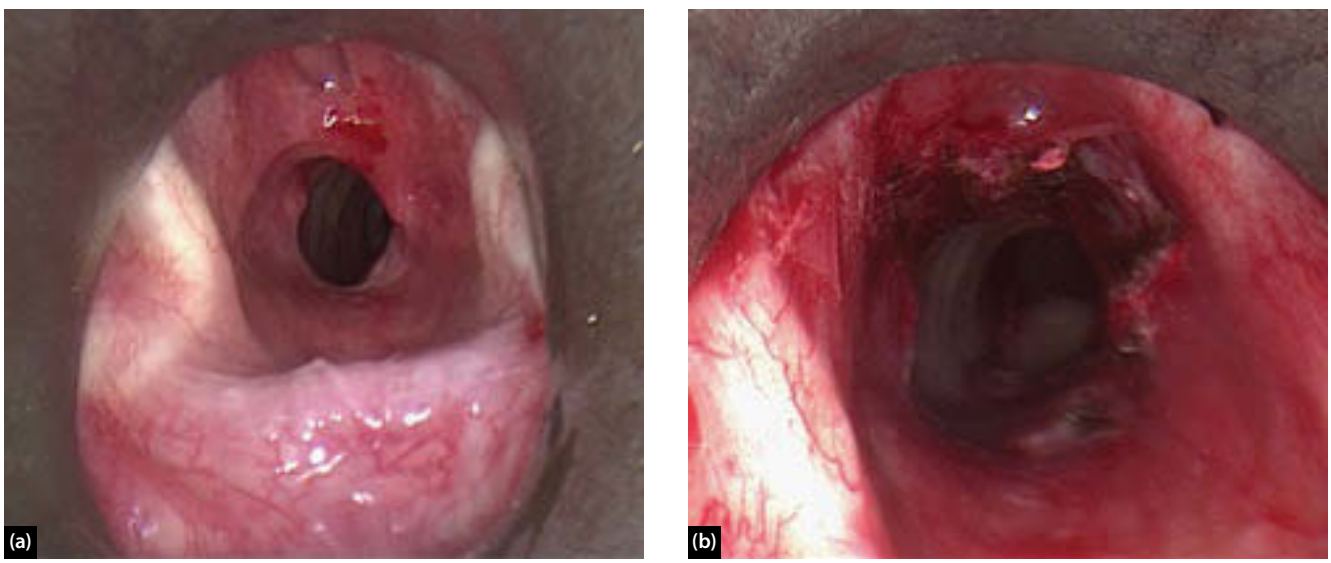

Figure 76.7 Idiopathic subglottic stenosis (a). The same lesion after steroid injection, radial cuts with the CO_2 laser and balloon dilatation **(b)**.

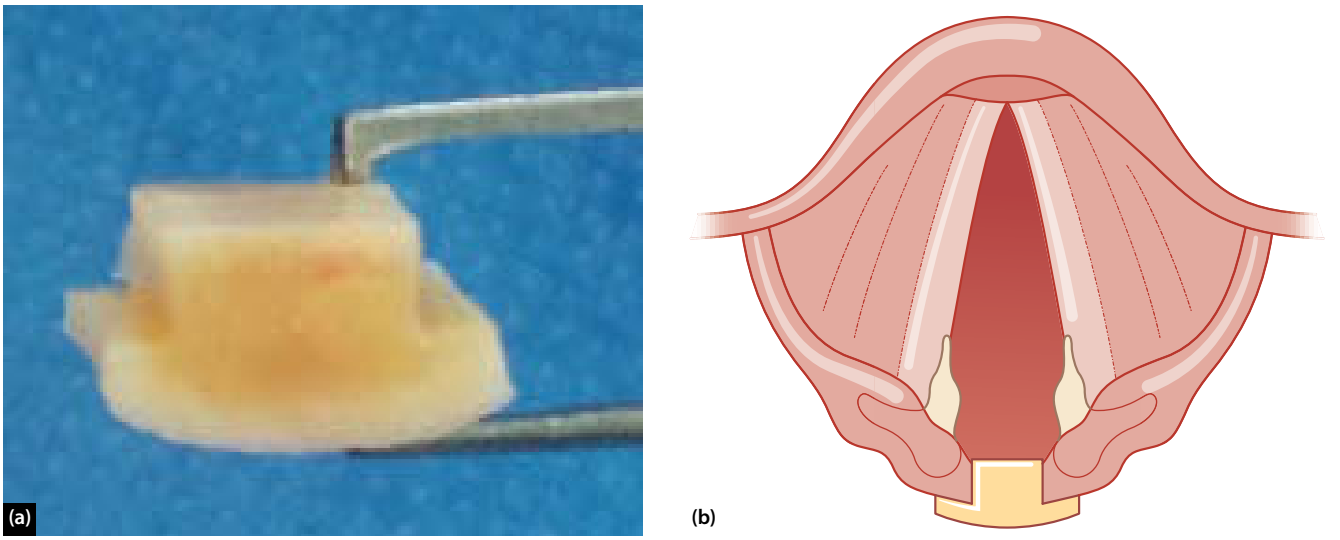

Figure 76.8 A costal cartilage 'spacer' (a), which is placed in a posterior cartilage split through a laryngofissure approach **(b)**.

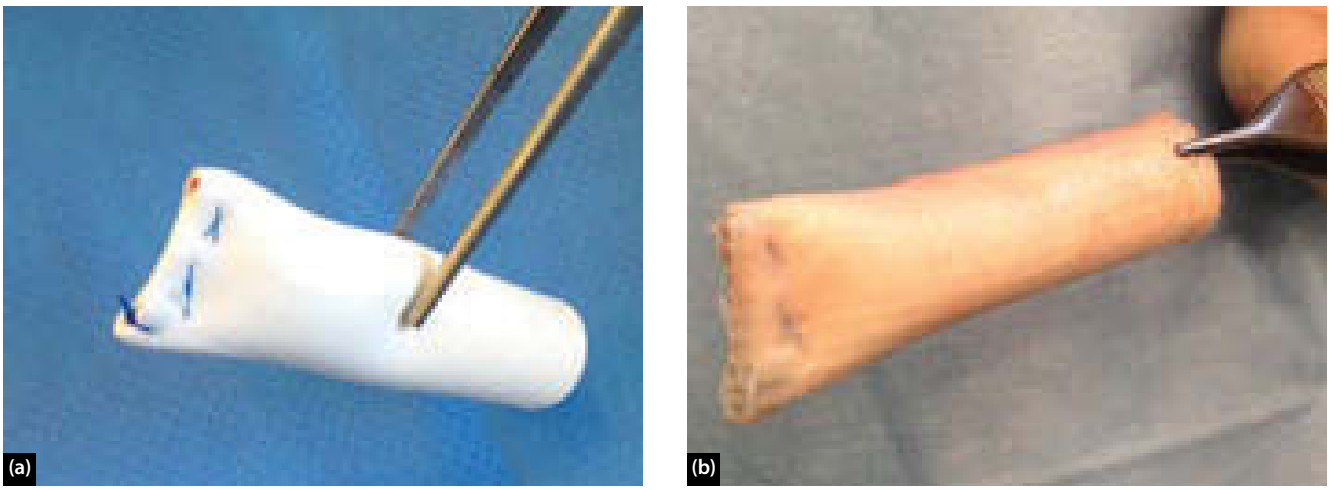

Figure 76.9 A section of silastic T-tube closed at one end with nylon suture (a). The same stent covered with superficial skin graft with epidermis against stent **(b)**.

A closed laryngeal stent, covered with a superficial skin graft is held in place with a single, strong, nylon suture.[20]

A temporary tracheostomy is required because there is no airway through the larynx once the laryngofissure is closed. Two weeks later the stent is removed endoscopically, followed by routine decannulation. The technique appears to work because keratinocytes colonize the parts of the airway where the diseased mucosa was excised and have a strong antifibrotic activity.

MITOMYCIN-C

Mitomycin-C (MMC) is derived from the *Streptomyces caespitosus* bacteria with the ability to modify wound healing at the molecular level and has been used to inhibit post-surgical scar formation. Available since the 1960s as a systemic chemotherapeutic agent in the treatment of solid tumours, MMC was first applied topically for the treatment of superficial bladder tumours. It was first reported in the ENT literature for the treatment of tracheal scarring after tracheal reconstruction in a small case series.[29] Several randomized prospective animal studies have shown impressive results in prevention of postoperative glottic and subglottic stenosis following surgery to the airway.[30–33] Its use in airway surgery has become fairly routine, despite no randomized controlled trials proving its efficacy. The authors have used MMC at concentrations of 1 mg/ml applied topically for 3 minutes in many hundreds of airway cases. Owing to lack of clear evidence of improved outcomes and continuing uncertainty about long-term toxicity we have stopped use of the drug.

GRANULOMATOSIS WITH POLYANGITIS

Granulomatosis with polyangitis (GPA) was formerly called Wegener's granulomatosis (WG) and is an immune disorder characterized by inflammation of small and

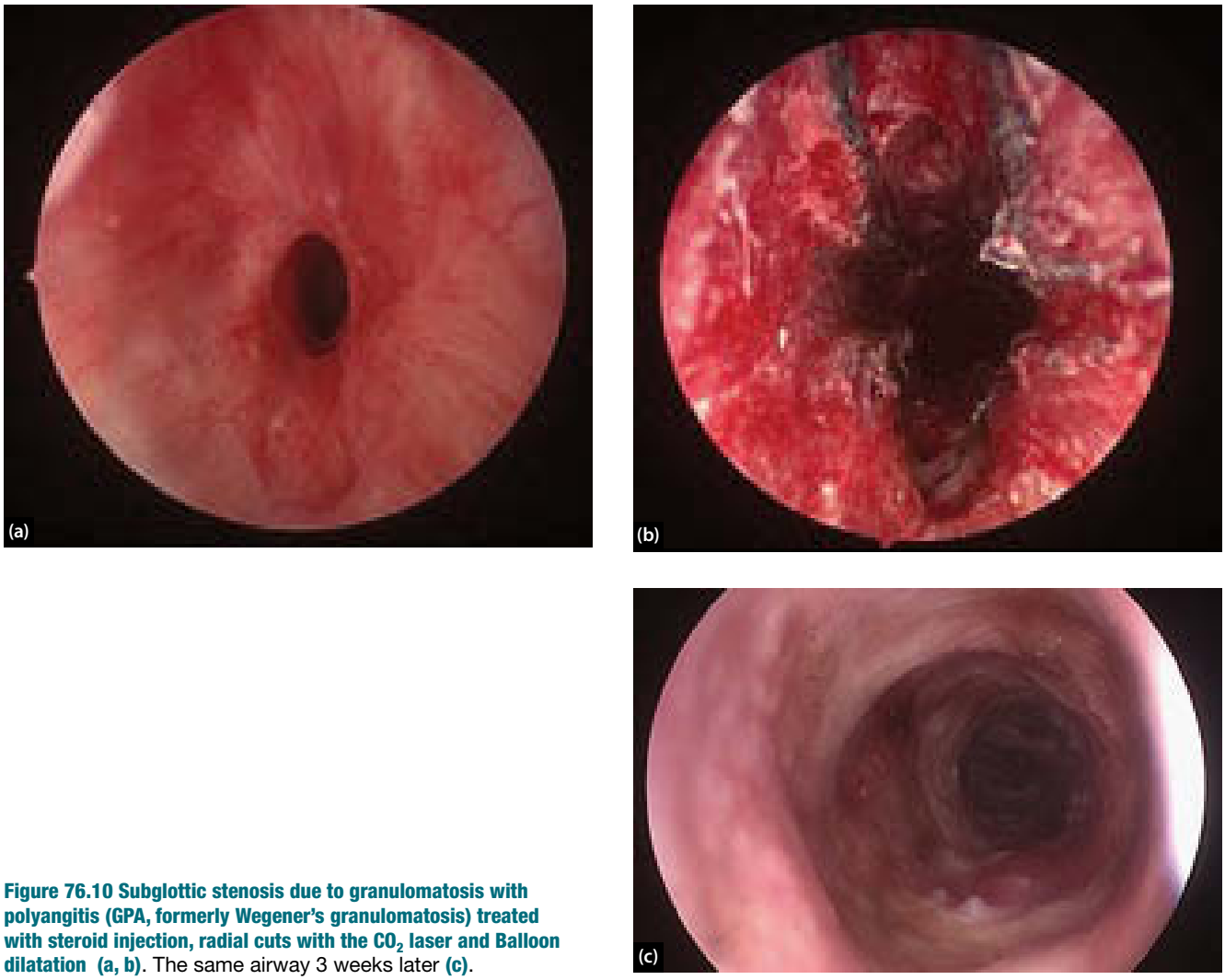

Figure 76.10 Subglottic stenosis due to granulomatosis with polyangitis (GPA, formerly Wegener's granulomatosis) treated with steroid injection, radial cuts with the CO_2 laser and Balloon dilatation (a, b). The same airway 3 weeks later **(c)**.

medium sized vessels. Most patients have some otolaryngological manifestations but also involvement of the lungs and kidneys and there may be an element of renal failure. The presence of a positive cytoplasmic antinuclear cytoplasmic antibody (cANCA) test may aid in the diagnosis, but positivity is not conclusive and negative ANCA results are not sufficient to reject the diagnosis. The diagnosis is sometimes made on clinical presentation when a patient has had the appropriate symptoms for a prolonged period. A definitive diagnosis of GPA can be made by a biopsy of suspicious lesions (demonstrating granulomatous inflammation) in conjunction with positive serological analysis. However, it must be recognized that up to 20% of patients with untreated active GPA lack cANCA[34] or may show positivity later on in the disease history.

Approximately 25% of patients have involvement of the larynx, trachea and bronchi causing localized narrowing. Intra-lesional corticosteroid injections, radiate lesion cuts and dilatation (**Figure 76.10**) will treat the majority of new stenoses.[35]

The use of tracheostomies and long-term stents can lead to airway complications that are difficult to treat.[10, 36]

SARCOIDOSIS

Cesar Boeck of Christiania, Denmark was the first to describe this multi-system disease in 1899.[37, 38] The disease is a non-caseating granulomatosis disorder with a worldwide distribution and can affect any race, ethnicity, gender or age group. Patients are typically aged 20–40 years, and there is a female to male ratio of 2 : 1 and a predilection for black African Americans.[38] Otolaryngologic involvement occurs in < 3% of cases and can occur in isolation or as part of a widespread disease.[39] Laryngeal sarcoidosis may be underdiagnosed and has a variable incidence reported between 1% and 5%.[40–43]

The pathophysiology behind sarcoidosis remains unknown. Current hypotheses propose sarcoidosis to occur in generally susceptible individuals through alterations in immune responses after exposure to various 'triggering' agents. The diagnosis of sarcoidosis depends on the presence of typical clinical features and non-caseating granulomatous inflammation on biopsy of diseased tissue with the exclusion of other known causes of granulomas, including tuberculosis, leprosy, syphilis and fungal disease.

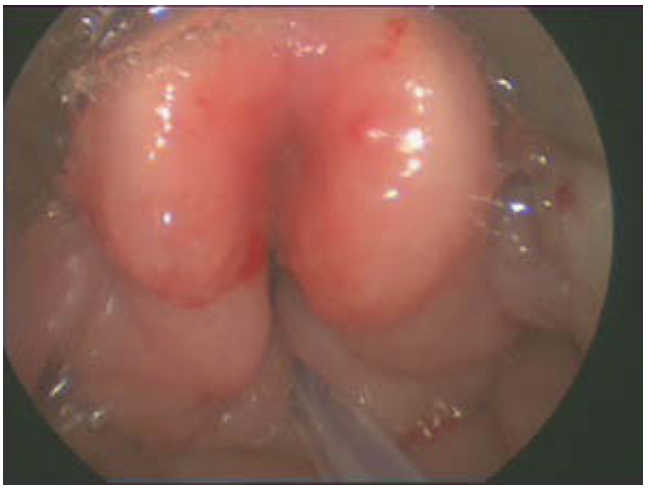

Figure 76.11 Supraglottic larynx in sarcoidosis. Demonstrating epiglottis and aryepiglottic folds 'swollen' with disease. Below is the subglottic jetting cannula in place during suspension laryngoscopy.

Anatomically, laryngeal sarcoid has a predilection for the supraglottic region, particularly the epiglottis, aryepiglottic folds and arytenoids (**Figure 76.11**). The macroscopic appearance of the supraglottis is diffusely thick, oedematous and characteristically pale or pink in colour. These features are considered pathognomonic for this condition.[40] Although exophytic, polypoidal, nodular and granulating lesions have been described, these are less common.[42] Isolated involvement of the glottis is exceedingly rare.[44] Vocal cord paralysis is also reported as a result of perineural invasion or multiple cranial nerve polyneuritis.[40] Laryngeal disease tends to progress slowly with a relapsing and remitting course. Macroscopically laryngeal lesions may appear to persist despite overall remission and this is thought to be due to tissue fibrosis.

High dose systemic steroids have been recommended as the first line treatment of laryngeal sarcoid. Endoscopic laser reduction has been used as a last resort where conservative therapy has failed. Our technique for managing laryngeal sarcoidosis has led to a reduction or cessation of systemic steroids and decannulation in the majority of cases.[45] The procedure is performed using total intravenous general anaesthesia with suspension laryngoscopy and a subglottic or supraglottic high frequency jet ventilation technique. The larynx and airway are visualized using a combination of microscope and a rigid optical endoscope. 1–3 ml Depo-Medrone (methylprednisolone acetate), at a concentration of 40 mg/ml, is injected into the lesion at multiple sites and evenly through its depth, using a microlaryngoscopy injection needle. The end point of injection should produce almost complete blanching of the lesion. Following infiltration volumetric lesion reduction is achieved using the carbon dioxide laser at a continuous setting of 8–10 W, delivered via the microscope. This brings about immediate airway improvements and the combination of healing and the steroid produce further reductions in disease bulk. Any pedunculated lesions encroaching into the airway are removed and sometimes radial 'releasing' laser cuts are necessary. It is important not to create a circumferential injury in or around the laryngeal inlet as this has the potential to produce airway narrowing through scarring. Multiple narrow pits are created with the CO_2 laser ('pepper pot' pattern) separated by 2–3 mm and extending to the depth of the lesion. Most patients require on average of two treatments (range 1–4) separated by 3–4 weeks.[45]

BILATERAL VOCAL CORD MOBILITY IMPAIRMENT

Bilateral vocal cord mobility impairment (BVCMI) can produce reasonable voice but with some degree of dyspnoea as the vocal cords tend to lie in the median or paramedian position. Bilateral abducted cords are usually seen in neurological conditions and management is aimed at preventing aspiration, see Chapter 56, Chronic aspiration.

There are three principal causes of impaired vocal cord function:

- bilateral laryngeal denervation (neck and chest malignancy or thyroid surgery)
- bilateral cricoarytenoid joint fixation (trauma or rheumatoid arthritis)
- inter-arytenoid scarring (following endotracheal intubation).

Surgery is directed at improving the aperture of the posterior glottis. For bilateral denervation injuries we have had significant success with an endoscopic partial posterior cordectomy and partial arytenoidectomy using the CO_2 laser. The resection can be unilateral or bilateral (**Figure 76.12**).

The voice does become 'breathier' but remains functional. Destructive laryngeal surgery should only be considered when the possibility of spontaneous recovery has been ruled out and the patient has a safe swallow. Where there is potential for recovery, and a severely compromised airway, a temporary tracheotomy may need to be considered or the use of vocal cord suture lateralization procedures,[46] each of which are reversible. Various reinnervation operations have been described and the most promising technique uses the accessory phrenic nerve and anastomosing to the posterior cricoarytenoid muscle.[47] Other groups are looking at reanimating the human larynx with implantable electrical stimulation devices.[48]

With fixed cricoarytenoid joints the only surgical option is some form of laser to the posterior cord or arytenoid as described above.

Posterior glottic injuries can result in interarytenoid scar tissue, which in turn can lead to cricoarytenoid joint ankylosis, unless identified and treated early. The most common cause for this type of injury is endotracheal intubation and this is a reason for early tracheostomies on the ICU. Attempts at repairing the posterior glottis have included posterior laryngeal mucosal flaps, advanced into the post glottis, after division of the scar tissue. Unfortunately, all the procedures to correct this problem

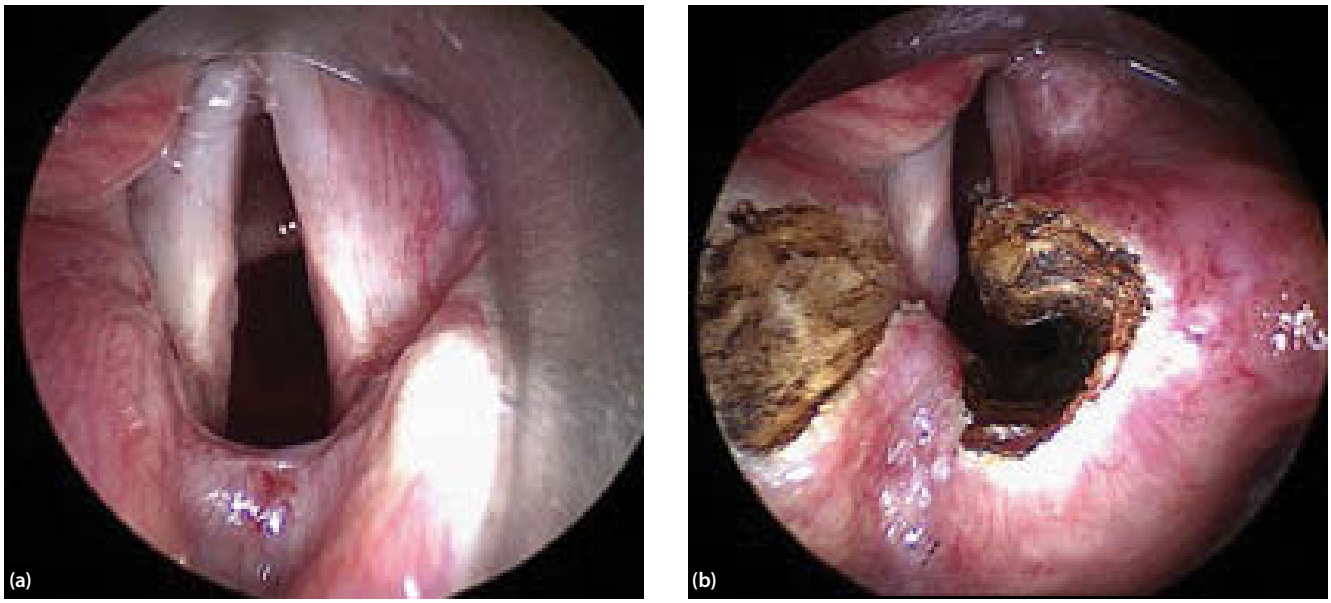

Figure 76.12 Larynx in bilateral cord palsy with the cords separated by the laryngoscope (a) Partial right laser arytenoidectomy with reduction of overhang from left arytenoid **(b)**.

lead to a compromise between voice airway and swallowing. Our preferred technique is the placement of a costal cartilage derived 'spacer' within a posterior cricoid split, through a laryngofissure approach.

FUTURE PROSPECTS

Up to 6 cm of trachea can be resected[17] in the adult with primary anastomosis. There is currently no solution to the repair of damaged tracheas beyond this length or where previous resections have failed. Tissue engineering[49] and tracheal allotransplantation[50] are two techniques that may provide future treatment options for these difficult cases. Laryngeal transplantation may be a solution to restoring the airway where this organ is dysfunctional or damaged beyond repair.[51]

Biotechnology may provide synthetic airways or scaffolds to deal with tracheomalacia and long length tracheal replacements in the more distant future. Biointegratable stents could be an even simpler solution for the management of airway stenosis.

Until these technologies are proven and widely available, prevention of laryngotracheal airway damage is important. This means appropriate sizing of endotracheal and tracheostomy tubes, monitoring cuff pressures and early change to tracheostomies in patients destined for prolonged ventilation. Also, early recognition and treatment of airway injuries, when they do occur, carries a greater chance of successful outcomes.

KEY POINTS

- The most common cause of laryngotracheal stenosis is a period of intubation and ventilation on the intensive care unit.
- The incidence of laryngotracheal stenosis is similar in patients who receive an earlier tracheostomy on the intensive care unit vs those that continue to be ventilated with an endotracheal tube. The difference is the stenosis is less likely to involve the glottis if the patient has a tracheostomy.
- Many of the cases of the stenosis due to systemic inflammatory diseases should and can be managed endoscopically, avoiding tracheostomies, stents and laryngotracheal reconstruction.
- Where an airway disease or trauma has damaged the cartilaginous framework of the larynx and trachea, endoscopic surgery is unlikely to restore a normal airway. These patients will usually require tracheal or cricotracheal resections, or laryngotracheal reconstruction.
- Airway stents are not a good long-term solution to laryngotracheal stenosis, as they are prone to migration, fouling and in the case of metal stents, fragmentation and granulation.

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CHAPTER 77

REFLUX DISEASE

Mark G. Watson and Kim Ah-See

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SEARCH STRATEGY

Data in this chapter may be updated by a PubMed search using the keywords: laryngopharyngeal reflux, extra oesophageal reflux, laryngeal reflux, silent reflux, acid laryngitis and globus pharyngeus.

INTRODUCTION

Laryngopharyngeal reflux (LPR), caused by the backflow of gastric contents into the upper aerodigestive tract, is frequently diagnosed as a cause of throat symptoms in ENT patients, although there remains a degree of controversy surrounding the subject. The condition was first described by Koufman in 1991.[1] Since then, there has been a wealth of excellent basic science research describing the underlying disease process, but the diagnosis and management of this condition is less clear.[2]

In the oesophagus, a degree of gastro-oesophageal reflux is considered physiologically normal, as long as the exposure time does not exceed 5% in 24 hours. Although the oesophagus is lined by resilient stratified squamous epithelium, the tissue damage is thought to be acid mediated; however, mechanisms exist that physically remove and chemically neutralize the refluxed bolus. A proportion of gastro-oesophageal reflux disease (GORD) patients (possibly as many as two-thirds) have a variant known as non-erosive reflux disease (NERD) in which frank oesophagitis is absent.[3] In classical GORD, reflux typically occurs in the supine position.

In contrast, the larynx is lined in part by areas of very delicate squamous epithelium, and elsewhere by respiratory epithelium, both of which are far less resilient than the oesophageal mucosa. Refluxate, when present, is neither removed by peristalsis nor neutralized by bicarbonate. Tissue damage is thought to be mediated by activated pepsin, and can occur very rapidly following exposure times, which may be as brief as 30 seconds 3 times per week.[1] Reflux disease that affects the laryngopharynx (LPR) is one form of extra-oesophageal reflux (EOR). LPR events often occur in the upright rather than supine position.

Although GORD and LPR may exist independently, as disease severity increases the likelihood of both types being present increases.[4]

This chapter will concern itself mainly with the management of LPR. Other forms of EOR have been described, including reflux-associated cough, nasal and sinus disease, and glue ear. Manifestations of reflux disease in paediatric ENT practice are described in Volume 2, Chapter 44, Reflux and eosinophilic oesophagitis.

PATHOPHYSIOLOGY

Gastric refluxate is often considered solely in terms of its acid content, but in addition to hydrochloric acid it also contains enzymes (notably pepsin), food residues, bile acids and bacteria. Reflux episodes may involve significant volumes of liquid gastric contents, particularly in the lower oesophagus, but in the laryngopharynx may be mainly gaseous, containing a fine aerosol of droplets.[5] Such episodes may be triggered by transient lower oesophageal sphincter relaxations. Once the aerosol has reached the laryngopharynx, it then has easy access to the nose, nasopharynx and lower respiratory tract.

Pepsin

Pepsin is secreted in the form of pepsinogen, which is physiologically inactive. It is activated by cleavage in an acid environment (pH < 4). It had long been thought that pepsin was only active in a highly acidic environment (pH < 4), but recent research using human rather than porcine pepsin shows that, once activated, significant activity remains almost up to neutrality (pH = 7).[6] Even at this level, the enzyme is not damaged, and can be reactivated by a fall in pH. It is not irreversibly deactivated until pH > 8. Pepsin binds to mucosa, and is even taken up into epithelial cells by endocytosis. If the pharynx or larynx is coated with refluxate after a reflux event, pepsin activity gradually decreases as the pH drifts toward neutrality, but can be quickly reactivated by another event, or by ingestion of an acidic bolus. Cola drinks, for instance, have a pH of < 2. As pepsin is active at higher pH levels than previously thought possible, investigation techniques that rely on a pH threshold of 4–4.5 may miss weakly acid or non-acid episodes that can cause tissue damage.

Other components of refluxate

Hydrochloric acid may be present in concentrations that can be affected by medication, notably proton pump inhibitors (PPI). Pancreatic proteases (especially trypsin) may be present, especially in patients who have had gastrectomy or gastroenterostomy, or who are taking PPIs. Bile acids are mainly in conjugated form, but free bile acids can cause tissue damage.[6] Partly digested food residues and bacteria, notably *Helicobacter pylori*, may have some relevance.

LPR DIAGNOSIS

Most patients with LPR are diagnosed on clinical grounds, following outpatient assessment including history taking and examination with flexible or rigid laryngeal endoscopy.[7] In the UK, further investigations for clinically diagnosed LPR are usually reserved for a subset of patients in whom the diagnosis is in doubt, or there is failure to respond to treatment.

SYMPTOMS

LPR symptoms are shown in **Box 77.1**. It is recommended that a structured symptom questionnaire is used at each consultation, and the score documented. The document in most widespread use is the Reflux Symptom Index (RSI).[8] Although it is fairly sensitive, it has limited specificity, as other conditions that produce laryngeal inflammation will also produce a high score. Other causes of laryngeal inflammation are shown in **Box 77.2**. It must always be borne in mind that LPR is only one cause of an inflamed larynx. Most patients with LPR will have a combination of throat symptoms, which will be demonstrated by the RSI. Those with a single symptom, for example globus pharyngeus, will produce a low RSI score and be less likely to have significant LPR (**Box 77.3**).

BOX 77.1 LPR symptoms

- Dysphonia
- Swallowing difficulty ('pseudodysphagia')
- Globus/feeling of lump in throat (FLIT/FOSIT)
- Throat clearing/tickle in throat
- Sore throat
- Cough/choking
- Thick mucus in throat, 'post nasal drip' or 'catarrh'
- Laryngospasm/cough syncope

BOX 77.2 Causes of laryngeal inflammation

- Reflux disease
- Smoking/inhaled irritants
- Alcohol
- Allergy
- Virus infections
- Voice abuse

BOX 77.3 RSI scores

Hoarseness or problem with your voice	0–5
Clearing your throat	0–5
Excess throat mucous or postnasal drip	0–5
Difficulty swallowing food, liquids or pills	0–5
Coughing after you have eaten or after lying down	0–5
Breathing difficulties or choking episodes	0–5
Troublesome or annoying cough	0–5
Sensations of something sticking in your throat or a lump in your throat	0–5
Heartburn, chest pain, indigestion or stomach acid coming up.	0–5

Score: 0, no problem; 5 a severe problem. Total score: >10 may indicate a problem with LPR[8], >20 moderate and >30 severe.

EXAMINATION FINDINGS

The clinical examination of a patient with symptoms suggestive of LPR will include an outpatient fibre-optic endoscopy of the larynx and hypopharynx.

A variety of features have been described as being attributable to the effects of LPR. In general, elements of erythema and/or oedema seen in various locations throughout the laryngopharynx may be caused by LPR.[9] These have been summarized in the Reflux Finding Score (RFS) (**Box 77.4**).[10] Each of the items is scored by an observer. Out of a potential score of 26, Belafsky et al. consider a score of >7 to indiceate LPR.[10]

Some authors report the RFS as demonstrating a reliable correlation with symptoms and response to treatment,[10] although there remains some controversy as to its reproducibility as an accurate tool as others report less reliable correlation.[9]

BOX 77.4 Reflux Finding Score (RFS)

- Infraglottic oedema (*pseudosulcus vocalis*)
- Ventricular obliteration
- Erythema/hyperaemia
- Vocal fold oedema
- Diffuse laryngeal oedema
- Posterior commissure hypertrophy
- Granuloma or granulation
- Thick endolaryngeal mucus

A review of data from meta-analyses reveals laryngeal mucosal findings in 38.2–51.2% of patients with symptoms of reflux laryngitis.[11]

Other studies, however, have noted these findings to be prevalent in the general population with a high rate of abnormal findings in asymptomatic people. A recent review of mucosal signs in LPR highlighted similar proportions of normal and patient populations with reported laryngeal mucosal changes – or increased RFS.[12]

Similarly, laryngeal abnormalities have also been reported in 64–86% of normal controls.[13] In addition, the non-specific nature of these signs means they can also be seen secondary to several other causes: smoking, infection, alcohol, allergies, asthma and voice abuse.[14] A recent study of asymptomatic singers identified a high percentage of laryngeal abnormalities, thus recommending caution when using mucosal signs alone to diagnose LPR.[15]

Similarly, laryngeal findings are seen in patients with GORD (18.9–85%) with posterior larynx and posterior pharyngeal wall findings being the most common.[11]

No single sign appears to be pathognomonic of LPR; however, the presence of pseudosulcus or Reinke's oedema in *symptomatic* patients may be an indicator of LPR. (Positive predictive value (PPV) 67–90% for pseudosulcus in the presence of laryngeal symptoms.)[16] Recent work also suggests a possible new sign of a mucosal white line in the nasopharynx may be useful in identifying the presence of reflux affecting the pharynx.[17]

There remains, therefore, a significant amount of controversy around the reliability of examination findings in making the diagnosis of LPR.[11] Clinical symptom reporting, including the use of symptom scores such as the RSI, may correlate better with this subjective condition.[18] While the use of RFS has shown some inter-rater reliability, one must exercise caution when using mucosal signs alone to make the diagnosis of LPR. Using these examination findings to complement information gained from clinical history and symptom scores, as well as a tool to monitor the patient response to treatment, is probably a more reasonable approach.

INVESTIGATIONS

Following appropriate clinical assessment supplemented by appropriate questionnaires, several investigations have been reported in LPR.

Imaging

Barium swallow has traditionally been used for assessment of throat symptoms, including globus pharyngeus and those associated with LPR. It is no longer very widely used in this setting as swallowing a large bolus of dense liquid on an empty stomach and then tilting the patient head down to see if reflux occurs is probably not physiologically representative of events in normal life. It is still useful if dysphagia for solids is present, and is the investigation of choice if pharyngeal pouch is suspected. Videofluoroscopy is a valuable investigation for neuromuscular swallowing disorders, but not usually for LPR.

Functional tests

The Bernstein acid perfusion test involves passing a nasogastric tube into the lower oesophagus and instilling 0.1 M hydrochloric acid solution. If the patient then reports chest pain similar to his/her symptoms, then this would confirm that the cause is GORD rather than cardiac disease. It is no longer used for this purpose but has re-emerged as a research tool in recent years for reflux-related lower respiratory tract symptoms.

Pepsin testing

As LPR is thought to be pepsin mediated, testing for its presence in the larynx and pharynx is a logical development. Biopsy specimens can be stained for the presence of pepsin, but this requires an invasive procedure and is not used outside research programmes. A test is now available for the presence of pepsin in pharyngeal secretions (Peptest; RD Biomed Ltd, Hull, UK). This test is entirely non-invasive, and is easy and relatively cheap to perform. The patient expectorates pharyngeal secretions into a specimen tube containing a citric acid buffer. After mixing and centrifugation, the specimen is placed on a test strip and read after approximately 15 minutes. A positive result is strongly predictive for the presence of LPR, although a negative result does not exclude.[19] Examination of more than one specimen for each patient may increase diagnostic accuracy. Pepsin can also be detected in nasal secretions and exhaled breath condensate in ventilated patients using the same technique.

Manometry

Although oesophageal manometry is not itself helpful in the diagnosis of LPR, it is usually performed prior to pH monitoring (see the next section) to identify the position of the upper and lower oesophageal sphincters to aid electrode placement. High-resolution techniques give more detailed information on oesophageal function. Some patients with symptoms of LPR who do not respond to treatment will be found to have oesophageal dysfunction as their underlying problem.[20]

pH and impedance monitoring

For some years the 'gold standard' investigation was thought to be 24-hour dual-channel pH monitoring, with electrodes at the level of the upper sphincter, and in the lower oesophagus just above the lower sphincter.[21] A range of normative values have been published, with some authors suggesting that 4 episodes/24 hours at the

upper electrode are required for LPR diagnosis, and others suggesting that a single episode is sufficient. In practice, many patients have multiple episodes, enabling the diagnosis to be made easily, with only a small number falling into the 1–4 episodes/24 hours range.

The main limitation of pH monitoring alone is that the pH threshold is set at pH4 or 4.5: this test will therefore fail to identify weakly acid (pH4.5–7) or non-acid (pH>=7) events. Multichannel intraluminal impedance (MCII) monitoring, which adds an array of electrical impedance electrodes to the test catheter, can be added to dual channel pH monitoring, and may increase diagnostic accuracy by recording all reflux events. Once again, normative data are not standardized and like pH monitoring, MCII is an invasive and expensive test that some patients cannot tolerate.

A less expensive and better-tolerated technique is airway pH monitoring (Restech; Respiratory Technology Corp., San Diego, CA, USA). This uses a small catheter with a probe placed at the level of the soft palate, which is used to produce a 24-hour recording. Although results were initially promising,[22] more recent work has cast doubts on the reliability of this method.[23]

TREATMENT

Possible treatments for LPR include dietary and lifestyle measures, medical treatments and antireflux surgery.

Diet and lifestyle

There is good evidence that alteration of diet and lifestyle can improve LPR symptoms,[24] and this aspect of treatment should be stressed to all patients. The main points are shown in **Box 77.5**. Consumption of alkaline water has recently been advocated but is as yet clinically untested.[25] An advice session from a suitably trained speech and language therapist (which may be delivered on a group or individual basis) can improve compliance[14] and, if hoarseness is a significant symptom, voice therapy can also help.[26] As well as giving patients written advice on lifestyle measures, online resources are also available.

Medical treatments

This is perhaps the most contentious issue in relation to LPR. There is, as yet, no drug that acts directly against pepsin, which is thought to be the causative agent. Drugs currently available to prevent reflux episodes and improve oesophageal function (metoclopramide, domperidone) are much less effective than cisapride, which is no longer available due to toxicity problems, and recently limitations have also been imposed on the use of domperidone. Antacids alone have little effect, and the role of acid suppressant drugs (particularly PPIs) is controversial,[27] with some authors advocating their use[28] and others claiming they are ineffective.[29] PPIs are the treatment of choice for patients with GORD, which is thought to be acid mediated, but in LPR their effect is at best indirect by raising gastric pH to reduce activation of pepsin by cleavage of pepsinogen. Simply telling a patient that their symptoms are due to LPR and issuing a prescription for PPIs is unlikely to achieve a good outcome. Barrier agents (such as alginate) can be used to protect the mucosa of the oesophagus and upper aerodigestive tract.

BOX 77.5 Diet and lifestyle advice

- Give up smoking.
- Reduce alcohol intake. Spirits, white and rosé wine are particularly irritant.
- Avoid carbonated drinks (even carbonated water) and fruit juice.
- Reduce caffeine intake.
- Avoid fatty foods (anything fried, chips, cheese, pastry, chocolate).
- Elevate the head of the bed at night.

Proton pump inhibitors

Proton pump inhibitors (PPIs) are in common usage for treatment of LPR, particularly as part of a combined management strategy including diet and lifestyle advice as described earlier. An example of such a strategy is given in **Figure 77.1**. Although clinical trials have so far produced conflicting results as to the benefits of using PPIs, they are cheap (in the UK, generic pantoprazole currently costs approximately £1.30 for a box of 20 mg tablets) and generally well tolerated, although diarrhoea may be more of a problem with lansoprazole than other agents. In longer-term use, and particularly in high dosage, increased incidence of pneumonia, *Clostridium difficile* infection and osteoporosis have been described.

PPIs exert their effect by blocking the production of H^+ by the gastric glands. In GORD, they are highly effective at controlling symptoms in once-daily dosage. As described above, this is an acid-mediated disease, and the oesophagus can tolerate an acid pH for up to 5% of each day.

In LPR, by contrast, the aim of PPI therapy in LPR is to prevent the activation of pepsin. As mucosal damage can occur with short-lived reflux episodes, 24-hour coverage is necessary, and twice daily dosage is needed to achieve this as the drugs currently available are only active for 12–14 hours after each dose. PPIs are most effective if taken before food, as the drug needs to be present in the plasma when the proton pumps of the gastric glands are activated. It is therefore recommended that, if used, PPIs are given 30 minutes before breakfast and evening meal. Symptomatic improvement may take much longer than in GORD, and so a treatment trial of at least 2–3 months is required. A total treatment time of approximately 6 months has been advocated for responders,[30] and with the recognition of acid rebound if PPI therapy is discontinued abruptly,[31] tapered withdrawal may be more appropriate (**Box 77.6**).

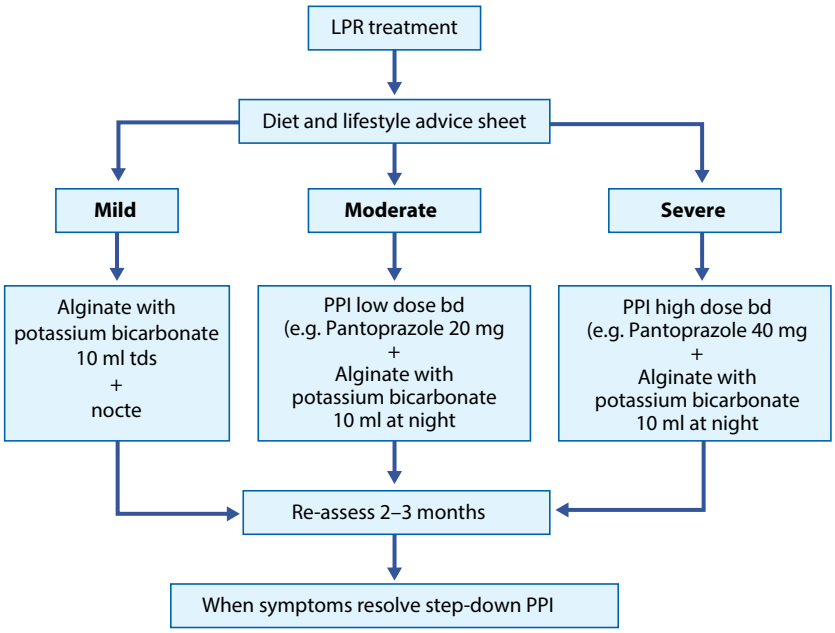

Figure 77.1 Combined treatment strategy.

BOX 77.6 PPI dose reduction schedule

- Pantoprazole 40 mg bd
  ↓ 2 months
- Pantoprazole 20 mg bd
  ↓ 2 months
- Pantoprazole 20 mg od
  ↓ 2 months
- Stop regular pantoprazole
- Consider providing a supply for prn use (e.g. before going out for a meal in a restaurant)
- Most patients do *not* need to be on long-term PPIs; only a small number need maintenance therapy.
- Gaviscon Advance and dietary advice are more suitable long-term measures in the treatment of reflux disease.
- Rebound symptoms are common on stopping PPI therapy; Alginate with potassium bicarbonate, 5 ml tds after meals and 10 ml at night for 2 weeks will help to reduce these.

Alginate

Alginate preparations have traditionally been used in the treatment of GORD symptoms such as heartburn, and there is evidence for the effectiveness in LPR of one alginate preparation that is currently available in the UK and Europe,[32] but not in the United States. Alginate is a non-systemic treatment derived from seaweed, and has little in the way of side effects, although some individuals find liquid preparations difficult to tolerate due to the thick consistency. Tablet formulations are available but the tablets are large and need to be sucked or chewed; they have a chalky texture.

Alginates are normally given after meals and/or just before retiring at night. They can also be used for breakthrough symptoms such as cough or globus. They may be helpful just before activities that can cause reflux, such as vigorous exercise or singing. They can be used as part of a combined management strategy involving diet and lifestyle advice and possibly PPI prescription, as described above.

MANAGEMENT OF NON-RESPONDERS

Published response rates to the medical therapies described in this chapter vary widely. For those patients who do not respond, the following need to be established:

- Is the diagnosis correct?
- Is the treatment regime reasonable, and is the patient complying with it?

If the diagnosis of LPR is not clear, then further investigations should be performed in order to confirm or refute it. Even if the diagnosis is clear, confirmation prior to referral for further management (particularly antireflux surgery) may be needed. Pepsin testing of pharyngeal secretions, 24-hour dual channel pH monitoring and MCII monitoring should be considered.

A recent study examined 23 consecutive treatment non-responders using MCII and high-resolution oesophageal manometry.[20] All patients had failed 3 months of high-dose twice-daily PPI therapy. Breakthrough acid reflux was found in 5/23 (22%) and significant non-acid or weakly acid reflux in 12/23 (52%). Active reflux disease was therefore present in 17/23 (74%) of the non-responders, with >80% of the reflux episodes occurring in the upright position. In addition, manometry showed significant oesophageal dysmotility in a 5/23 (22%).

Therefore, it is clear that many patients who fail medical treatment do actually have LPR. A close check should be made on the treatment regime to confirm compliance. Has the patient complied with diet and lifestyle measures (**Box 77.5**)? In particular, check smoking status and consumption of alcohol, carbonated drinks (especially cola), fruit juice and acidic fruits, as well as sleeping position. Has the prescribed medication been taken as instructed, in adequate dosage and for a sufficient period? With PPIs, some patients may respond better to one drug than another, so trial of a different agent can be considered. If alginate has not been used so far, it can be prescribed. If there is significant reflux present and the patient has persisting symptoms, referral to a gastrointestinal surgeon for antireflux may be appropriate.

ANTIREFLUX SURGERY

Surgery for reflux disease usually involves one of several forms of laparoscopic fundoplication, although some procedures implant a prosthesis to prevent reflux episodes.

Surgery may be considered either for LPR that does not respond to medical treatment, or for patients who require long-term high-dose PPI treatment to control symptoms, particularly at a young age. Surgery has been shown to produce better results in those who have GORD symptoms as well as LPR, or who have positive findings on pH monitoring, as well as those who respond well to PPIs.[33]

FUTURE RESEARCH

➤ Management of LPR patients will be improved when the diagnosis can be made with confidence by means of quick, cheap, reliable non-invasive tests, and medical treatments are available that prevent the activation or function of pepsin. Development of clinical guidelines would help to standardize treatment at an acceptable level.[34]

KEY POINTS

- Laryngopharyngeal reflux may cause throat symptoms.
- The evidence base is limited.
- Acid and pepsin are present in the refluxate.
- Symptoms and examination findings are subjective.
- Lifestyle changes and anti-reflux medication may help.
- Anti-reflux surgery may be considered in resistant cases.

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CHAPTER 78

PARALYSIS OF THE LARYNX

Lucian Sulica and Babak Sadoughi

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Unilateral vocal fold paralysis 1103
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Vocal fold paresis 1109
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SEARCH STRATEGY

Data in this chapter may be updated by a Medline search using the keywords: vocal fold paralysis, recurrent laryngeal nerve, laryngoplasty, thyroplasty, and laryngeal re-innervation, and focusing on evaluation and management.

INTRODUCTION

Paralysis of one or both vocal folds may impair the important physiologic functions of the larynx: breathing, swallowing and voicing. Individuals with laryngeal hemiparalysis typically complain of a broad range of symptoms reflecting variable degrees of glottic insufficiency. The most prominent of these are breathy dysphonia and dysphagia, particularly to liquids. Breathlessness while speaking and breathlessness during physical exertion may also be present. When both vocal folds are affected by the paralytic process, patients generally complain of symptoms of glottic obstruction such as stridor and dyspnea. This distinction in symptoms between unilateral and bilateral paralysis reflects the contrasting valving tasks of the larynx: glottic opening for respiration and glottic closure for airway protection, thoracic stabilization during effortful activity, and phonation.

The first important clinical task is establishing the cause of paralysis if possible. Effective management of symptoms follows. Some cases of paralysis improve symptomatically without intervention, while others fail to recover. Distinguishing between these two groups remains a challenge, and many otolaryngologists consequently choose to delay treatment until the possibility of spontaneous recovery is judged remote.

PATHOPHYSIOLOGY

Most cases of laryngeal paralysis result from peripheral nerve damage. Because the degree and pattern of neurological impairment varies, laryngeal paralysis is a heterogeneous condition with respect to symptoms, vocal fold position and electromyographic evidence of the degree of nerve damage.[1, 2] Unless due to severe trauma-like transaction, each case differs from the next in degree of neurologic impairment, and features a mix of injury types among its nerve fibres. This latter aspect is a principal reason why standard classifications of peripheral nerve injury are not entirely useful in vocal fold paralysis.

Both human and animal studies have shown that the larynx has a strong propensity for re-innervation,[2–4] which appears to be the rule rather than the exception. However, regeneration of the recurrent nerve is more problematic than that of most peripheral nerves because it carries a mixed population of adductor and abductor fibres. Re-innervation is often dysfunctional and does not yield physiologic motion. This neural dysfunction extends beyond traditional notions of synkinesis, in which balanced co-contraction of adductor and abductor fibres were theorized to produce an absence of net vocal fold motion. In fact, dysfunctional re-innervation may also occur when nerve regrowth is appropriately directed but insufficient, which may result in decreased force of contraction, loss of motor unit specificity, increased muscle fatigability and possibly changes in peripheral and central neural organization.[5] Nevertheless, the natural tendency for re-innervation accounts for the general trend for voice to improve over time in unilateral paralysis. Because of the predominance of adductor fibres, re-innervation tends to restore or preserve muscle bulk and tone, occasionally to the point that phonatory glottic closure is restored and conversational

voice sounds normal despite persistent vocal fold immobility. This explanation, well supported by electrophysiologic evidence,[1, 2] is probably closer to reality than the notion of gradual contralateral compensation.

For most of the last century, vocal fold position was erroneously thought to reveal the site or type of lesion, a prevailing belief that has since been invalidated by careful clinical and laboratory work.[6–8] Differing degrees and patterns of innervation probably account for variability in the position of the paralyzed vocal fold.

AETIOLOGY OF LARYNGEAL PARALYSIS

Most sources of nerve injury fall into three broad categories: mechanical damage from surgery or other trauma; functional compromise from a range of medical conditions; and other factors yet to be completely identified, designated 'idiopathic'.

The reported relative frequency of causes of laryngeal paralysis varies considerably (**Table 78.1**). In most series, laryngeal paralysis tends to affect men more often than women, probably reflecting the underlying gender distribution of thoracic malignancy. Uniformly, the left vocal fold is affected more often than the right, in approximately a 60:40 ratio or greater, due to the greater length and more profound descent into the thorax of the left-sided nerve, and its consequent greater vulnerability to disease and surgery.

Iatrogenic sources of injury have multiplied over time. In addition to thyroidectomy, still a main source of iatrogenic laryngeal paralysis, anterior approach to the cervical spine, carotid endarterectomy, and various cardiac and thoracic procedures have all become significant sources of laryngeal nerve injury (**Table 78.2**). The potential for recurrent nerve damage from the cuffed endotracheal tube is recognized and continues to account for cases of vocal fold immobility that are demonstrably neural in origin rather than the result of cricoarytenoid joint disruption.

A number of neurologic conditions remain relevant, albeit unusual causes of laryngeal paralysis. In contrast to other causes, some of these may be through a central mechanism. Vocal fold paralysis may appear in the wake of a stroke, almost always in conjunction with other deficits. Lateral medullary infarct (Wallenberg syndrome) is a complex of neural injury featuring vocal fold paralysis, dysphagia, vertigo, ataxia, Horner syndrome and hemifacial sensory deficit and/or pain. The vocal fold paralysis tends to improve with time, although measures may be needed in the short term to prevent aspiration. The vocal fold paralysis of Arnold-Chiari malformation tends

TABLE 78.1 Causes of unilateral vocal fold paralysis

Study	Year	N	Tumour	Trauma	Idiopathic	Other
Laccourreye et al.[9]	2003	325	9%	75%	12%	–
Loughran et al.[10]	2002	77	52%	22%	12%	5% intubation
Yumoto et al.[11]	2002	422	19%	33%	22%	8% intubation
Ramadan et al.[12]	1998	98	32%	30%	16%	11% intubation
Benninger et al.[13]	1998	280	25%	35%	20%	8% intubation
Bruggink et al.[14]	1995	215	25%	43%	18%	–
Yamada et al.[15]	1983	519	17%	12%	41%	11% intubation
Tucker[16]	1980	210	22%	42%	14%	–
Hirose[17]	1978	600	7%	37%	41%	2% intubation
Parnell, Brandenburg[18]	1970	100	32%	32%	10%	11% medical
Clerf[19]	1953	299	38%	20%	12%	9% medical
Work[20]	1941	183	14%	39%	23%	15% medical
Smith et al.[21]	1933	173	27%	16%	17%	36% medical

Adapted with permission from Sulica et al.[22]

TABLE 78.2 Surgeries and procedures that place laryngeal nerves at risk

Cervical surgery	Thoracic procedures	Other surgery	Other medical procedures
• Thyroidectomy/parathyroidectomy • Anterior approach to the cervical spine • Carotid endarterectomy • Implantation of vagal nerve stimulator • Cricopharyngeal myotomy/repair of Zenker diverticulum	• Pneumonectomy and pulmonary lobectomy • Repair of thoracic aortic aneurysm • Coronary artery bypass graft • Aortic valve replacement • Esophageal surgery • Tracheal surgery • Mediastinoscopy • Thymectomy • Ligation of persistent ductus arteriosus • Cardiac and pulmonary transplant	• Skull base surgery • Brainstem surgery, or neurosurgery that requires brainstem retraction	• Central venous catheterization • Endotracheal intubation

to be bilateral, and it is important to recognize promptly because it is reversible with timely hindbrain decompression. Charcot–Marie–Tooth disease and its variants are a heterogeneous group of hereditary motor and sensory neuropathies that may involve the laryngeal nerves. Neural compromise of the vocal fold appears to evolve slowly but relentlessly and is usually bilateral. Postpolio syndrome, a degenerative neurologic condition seen many decades after the acute disease, may present as a complex of bulbar deficits resulting in dysphagia, dysphonia and dysarthria. A similar presentation may be seen in multisystem atrophy, a degenerative parkinsonian condition where laryngeal neurologic dysfunction may contribute to mortality by creating respiratory obstruction. Laryngeal weakness may also figure in oculopharyngeal dystrophy and inclusion body myositis, although the mechanisms of nerve involvement are not fully understood in those conditions.

The incidence of idiopathic paralysis had remained approximately unchanged over the past century, unaffected by the introduction and refinement of computed tomography and magnetic resonance imaging. Based on serologic studies, cases have been attributed to Lyme borreliosis, herpes zoster and simplex, Epstein–Barr virus and even the West Nile virus. However, the cause of many cases of vocal fold paralysis in which serologies are normal and there is no history of antecedent viral disease are yet to be elucidated.

UNILATERAL VOCAL FOLD PARALYSIS

Clinical evaluation

HISTORY

Patients with unilateral laryngeal paralysis typically experience hoarseness and hypophonia. These can range from subtle vocal fatigue to near-total aphonia, reflecting the degree of glottic insufficiency, which varies from affected individual to individual. Dysphagia with possible frank aspiration may also be reported, albeit less often than voice complaints. Dysphagia-related complaints are more frequent in cases of 'high' vagal injury, affecting both superior and recurrent laryngeal nerves, which adds hemilaryngeal anaesthesia, pharyngeal constrictor atony and cricopharyngeal muscle hyperfunction to glottic insufficiency from the immobile vocal fold. Situations in which laryngeal anaesthesia exists alongside other cranial nerve deficits, as in jugular foramen syndromes, after stroke and after skull base surgery also carry increased dysphagia risk. Surgeries affecting pulmonary reserve, as do most thoracic procedures, appear to carry a higher risk of aspiration, and age may be an independent risk factor.[23]

Some patients will demonstrate a characteristically 'wet' vocal quality arising from pooled secretions, which interfere with phonation. By definition, such secretions have at least penetrated into the laryngeal introitus; these patients should attract the otolaryngologist's attention as being at risk for aspiration. More subtle symptoms include laryngospasm resulting from reaction to unexpected penetration or aspiration. This may occur in patients with surprisingly small degrees of glottic insufficiency and reasonably good voice quality.

Occasionally, patients may complain of phonation- or activity-induced shortness of breath. Careful questioning will reveal that this is not obstructive dyspnea, but rather breathlessness that results from excessive air escape during voicing, or from compromise of the thoracic fixation (Valsalva) manoeuvre during effortful activity. Pulmonary function testing will inevitably reveal an extra-thoracic obstruction; this, plus a lack of insight into laryngeal physiology, may lead the physician away from laryngeal intervention.

The otolaryngologist should also inquire regarding smoking history, the most recent chest imaging, and antecedent illness. A review of systems should focus on conditions likely to affect the larynx. Relevant factors include: neurologic symptoms like weakness, tremor and dysarthria; pulmonary symptoms suggestive of tuberculosis or malignancy; and exposure to neurotoxic agents like solid tumour chemotherapy (vincristine, vinblastine and cisplatin) or organophosphates found in pesticides. Unilateral vocal fold immobility is rarely mechanical in nature, but the possibility should not be dismissed in cases that are identified in the wake of clearly traumatic intubation or external trauma, or in the presence of arthralgias or known inflammatory joint disease.

PHYSICAL EXAMINATION

The examination should include palpation of the neck for lymphadenopathy or thyroid enlargement. The remaining cranial nerves should be evaluated, with special attention to the spinal accessory and glossopharyngeal nerves, which share the jugular foramen with the vagus. Other branches of the vagus should be examined as well. Finally, the presence of ipsilateral tongue deviation, palate droop or Horner syndrome should raise the suspicion of a cranial base lesion.

The larynx itself should be examined across a variety of laryngeal tasks. Flexible nasolaryngoscopy probably offers a more accurate impression of laryngeal function than rigid techniques, as the tongue traction necessary for the latter probably introduces some confounding biomechanical factors.

A hypomobile vocal fold may occasionally be difficult to appreciate; in such cases, asking the patient to alternate sustained vowel phonation and sniffing ('eee-sniff' manoeuvre) should bring any asymmetry into evidence. The examiner should not be misled by small amounts of vocal fold motion that may be caused by the interarytenoid muscle, receiving innervation from the contralateral nerve, by an intact cricothyroid muscle, or even by passive lateral displacement of the denervated arytenoid by its pair during adduction.

We have seen that the position of the paralyzed vocal fold carries no significance with respect to the site of the injury or prognosis. Nevertheless, careful examination can reveal features that may inform clinical care. Occasionally, increasing tension and length of the paralyzed vocal fold upon raising the pitch of the voice may

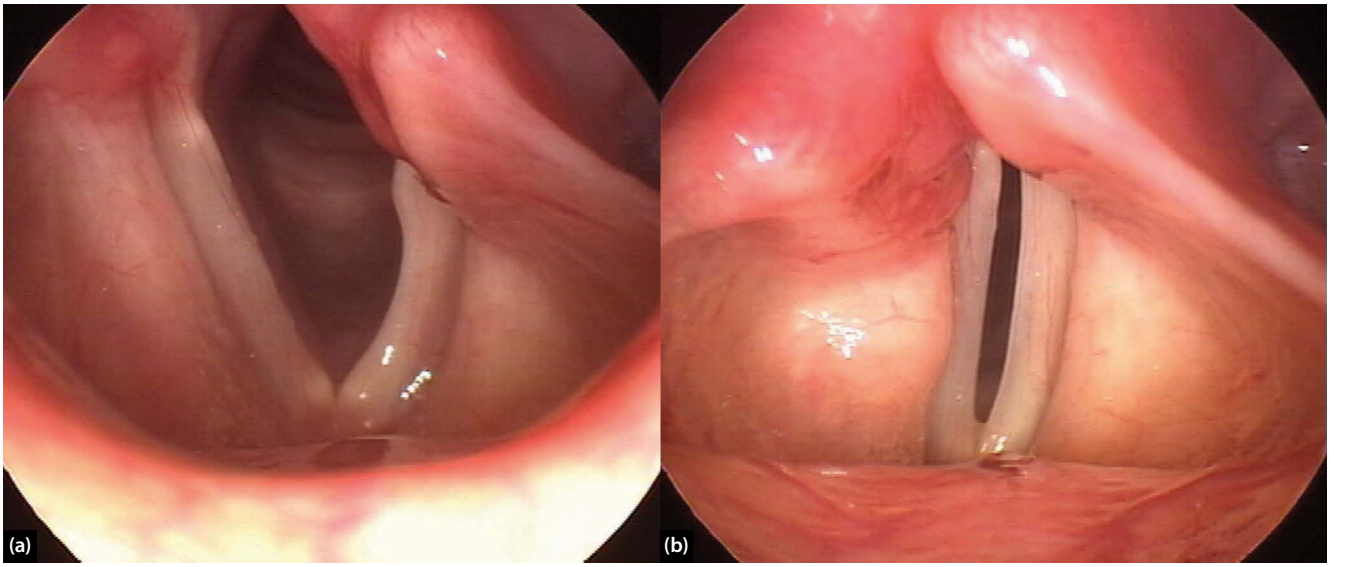

Figure 78.1 In this case of left vocal fold paralysis following anterior approach to the cervical spine, comparison of left vocal fold tension during quiet respiration (a) and phonation **(b)** suggests the superior laryngeal nerve is intact.

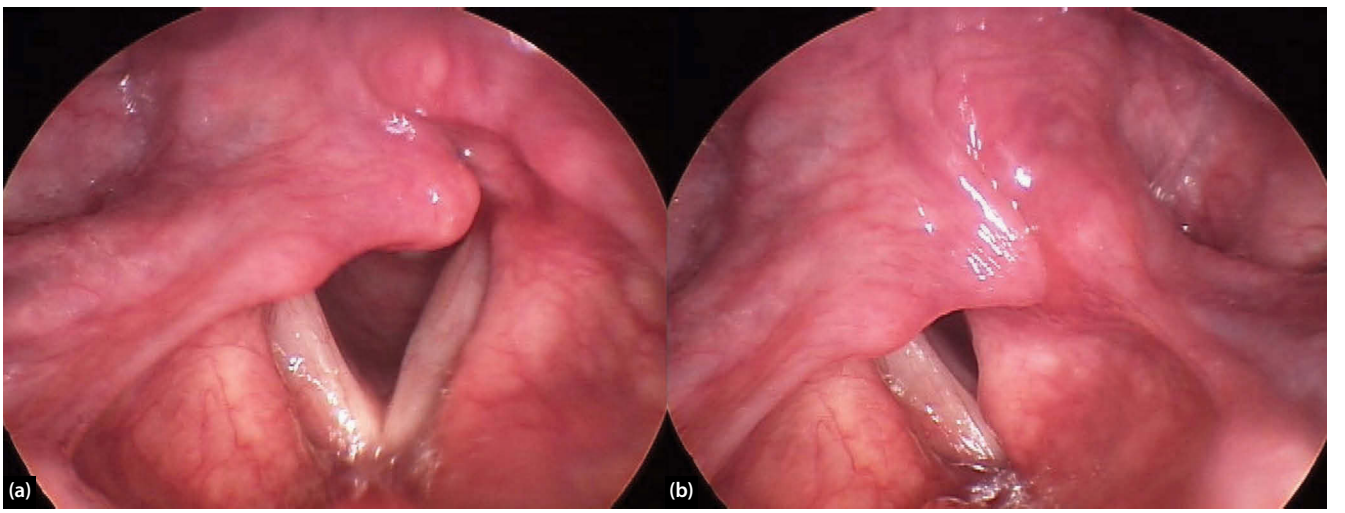

Figure 78.2 The right arytenoid is prolapsed into the laryngeal introitus in this case of idiopathic vocal fold paralysis, confirmed by electromyography (a). In adduction **(b)**, it interferes with the opposite cartilage and impedes closure. Rehabilitation without arytenoid repositioning surgery would very likely be suboptimal.

suggest an intact superior laryngeal nerve. Sometimes, patients may take advantage of intact cricothyroid function to improve voice projection by increasing vocal fold resistance to exhaled air (**Figure 78.1**); this pitch-raising phenomenon generates a characteristic voice described as 'paralytic falsetto'. The presence of supraglottic hyperfunction during phonatory effort should raise the possibility of glottic insufficiency. The ventricular folds serve as an accessory valving mechanism that tends to be engaged without deliberate effort when the vocal folds proper do not close effectively.[24]

Vocal fold adduction and abduction do not take place in two dimensions; the folds tend to abduct in a cephalad direction (into the ventricles) and adduct caudally. Thus, a paralyzed vocal fold may not rest in the same plane as its partner. Such three-dimensional judgements are difficult to make on laryngoscopy, but height mismatch is important to identify, as simple medial displacement of the paralyzed fold may not suffice for proper apposition during phonation.

Asymmetry of the arytenoids, with displacement of the cartilage on the paralyzed side forward into the laryngeal introitus (i.e. a 'prolapsed arytenoid'), is not a rare finding in laryngeal paralysis (**Figure 78.2**). This is not a sign of cricoarytenoid dislocation but does, however, suggest profound denervation with loss of muscular support for the cartilage. In addition, it strongly suggests a height and tension mismatch between the vocal folds. These factors argue for an arytenoid stabilization procedure should surgical rehabilitation be contemplated.

The incidence of cricoarytenoid dislocation as a cause of vocal fold immobility has been the subject of much debate. Experimental study has shown the cricoarytenoid joint to be strikingly robust and resistant to disruption.[25–27]

A problem-free intubation is unlikely to cause a joint injury, which usually follows obvious trauma, be it from intubation or external sources. The presence of arytenoid oedema and erythema, and the absence of a 'jostle sign' are suggestive of cricoarytenoid joint injury and should prompt further investigation (The Jostle sign is when the arytenoid cartilage on the side of the paralyzed cord, is passively displaced laterally on contact with the arytenoid on the normal side during phonation).

In hemilaryngeal paralysis, the glottal gap may be of two principal configurations. It may be essentially spindle-shaped, involving principally the membranous portion of the vocal fold, or V-shaped, marked by greater distance between the vocal processes of the arytenoid cartilages (**Figure 78.3**). This latter configuration is called a posterior gap, although the term does not refer to the absolute distance between vocal processes. The presence of a posterior gap should also cause the otolaryngologist to consider an arytenoid stabilization procedure for rehabilitation because implant medialization alone or injection augmentation is predictably poor at correcting this deficit.

Although there is no single metric of severity of symptoms of vocal fold paralysis, several simple clinical tools may help grade features of the history and examination. The Voice Handicap Index (VHI) and the voice-related quality of life (V-RQOL) are validated patient-completed self-rating scales that measure various aspects of vocal disability. The Consensus Auditory Perceptual Evaluation of Voice (CAPE-V) and the older grade, roughness, breathiness, asthenia, strain (GRBAS) scale are perceptual scales completed by the healthcare professional based on voice quality. The maximum phonation time (MPT) is the longest duration of sustained vowel phonation; for example, typically an /i/, which the patient can sustain, and is approximately inversely proportional to the degree of glottic insufficiency. The s/z ratio compares the MPT of a voiced (/z/) and unvoiced (/s/) sound. Under normal circumstances, the duration of the unvoiced sound should far exceed that of the voiced (the s/z ratio should be large), but with glottic insufficiency, the duration tends to become approximately the same (the s/z ratio tends to decrease).

ADDITIONAL INVESTIGATIONS

Fundamentally, diagnostic testing beyond the history and physical is intended to uncover causes of vocal fold paralysis. In cases temporally related to surgery that places the vocal folds at risk, no additional investigation is required. In others, malignancy is the principal pathology not to be overlooked. Imaging of the entire course of the affected laryngeal nerves is obligatory, including the mediastinum and the pulmonary apices.

Computed tomography (CT) from base of skull *through* the arch of the aorta or the right subclavian, as appropriate, is the minimum recommended study for laryngeal paralysis. In cases where a 'high vagal' paralysis is suspected according to criteria reviewed earlier, magnetic resonance imaging (MRI) may offer a more reliable means of imaging the skull base or central nervous system.

While serologies used to be ordered routinely, systematic examination has demonstrated a 0% yield in a series of 84 patients;[28] therefore, serologic testing is probably useless unless there is a specific clinical suspicion of an underlying illness.

Modified barium swallow is useful if a question of aspiration exists. The potential of morbidity related to dysphagia is a key element in determining the need for treatment.

Laryngeal electromyography (LEMG) measures the integrity of laryngeal innervation by means of percutaneous needle electrodes. It can provide unambiguous evidence of denervation and re-innervation, yet its utility in cases of vocal fold paralysis has been hotly debated. LEMG has been criticized for being a subjective study. In this respect, however, it does not differ

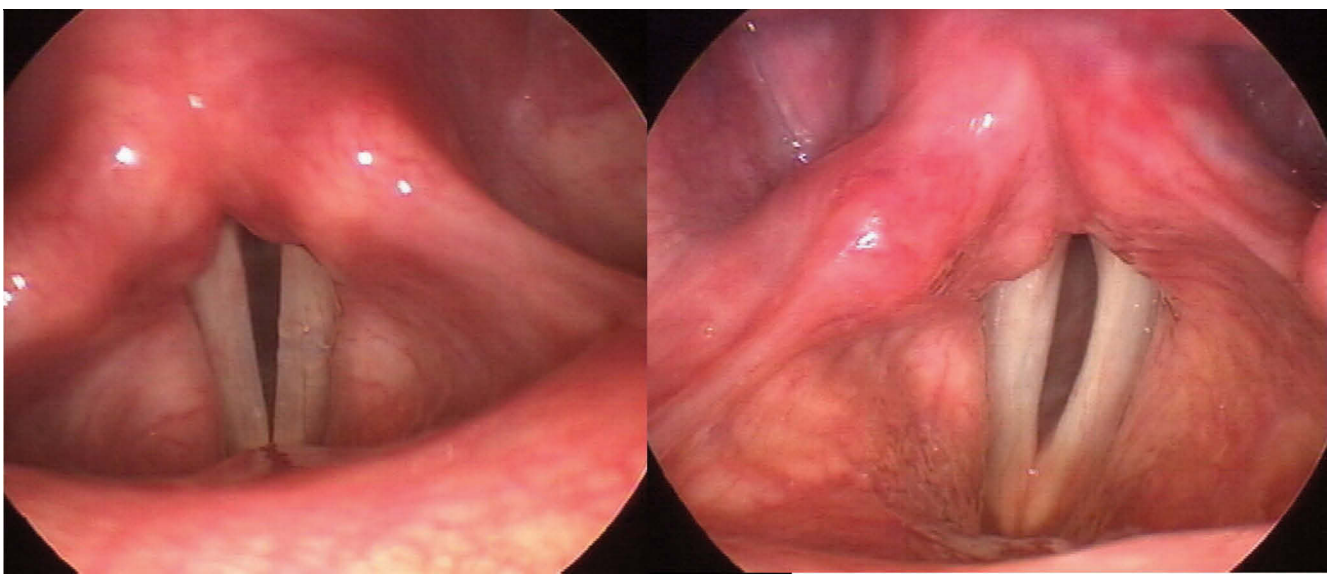

Figure 78.3 The case on the right, a left vocal fold paralysis following a thyroidectomy, demonstrates a posterior gap. On the left, a vocal fold paralysis from malignant mediastinal lymphadenopathy, closure at the vocal process is good. Compare also with the case in **Figure 78.2**, which also demonstrates a posterior gap.

TABLE 78.3 Laryngeal electromyography and prognosis in vocal fold paralysis of less than 6 months duration

Study	N	Accurate prediction of recovery	Accurate prediction of no/impaired recovery
Munin et al.[30]	31	80%	80%
Sittel et al.[31]	111	13%	94%
Gupta & Bastian[32]	18	70%	75%
Hirano et al.[33]	29	63%	80%
Parnes & Satya-Murti[34]	18	80%	100%

Adapted with permission from Sulica et al.[22]

from laryngoscopy and stroboscopy, except inasmuch as training and familiarity has allowed otolaryngologists to use these latter modalities more comfortably. In fact, LEMG exceeds both of these in its ability to definitively and objectively diagnose vocal fold paralysis, as opposed to immobility.

The practical clinical difficulty in the use of LEMG for prognosis has been that the appearance of electromyographic signs of re-innervation does not always lead to a return of vocal fold function, for pathophysiologic reasons reviewed earlier. Therefore, the utility of LEMG in prognosis in cases of vocal fold paralysis has been uneven. The available literature suggests that LEMG may be more useful as a predictor of poor outcome (**Table 78.3**), principally because electromyographic signs such as fibrillations and positive sharp waves, providing evidence of an absence of re-innervation, offer no physiologic ambiguities.[29] For now, LEMG clearly offers a reliable way to distinguish neurogenic from mechanical vocal fold immobility, and may offer variable prognostic information when used less than 6 months from the onset of paralysis.

Treatment

The management of glottic insufficiency in unilateral vocal fold paralysis is guided by concerns regarding morbidity from dysphagia and aspiration, the patient's own perception of the severity of the vocal handicap, and expectations about the eventual outcome without treatment. In turn, outcome expectations are influenced by the apparent cause of the paralysis and the time elapsed since onset.

OBSERVATION

Patients with hemilaryngeal paralysis, especially of short duration, may simply be observed. Factors favouring observation include:

- no evidence of aspiration
- injured laryngeal nerve(s) is (are) structurally intact and potential for recovery remains
- minimal vocal disability and/or minimal vocal demand
- comorbidities that discourage or prevent intervention.

Voice and swallowing therapy may be used as needed during the observation period. As with many interventions for this condition, the natural tendency of glottic insufficiency to improve over time makes it difficult to evaluate efficacy, and there is no convincing evidence that voice therapy affects the course and symptoms of vocal fold paralysis. Nevertheless, a skilled voice therapist may offer the patient insight into the condition.

The presence of severe dysphagia, history of aspiration pneumonia or observed aspiration during clinical evaluation effectively trumps other factors and demands intervention.

INJECTION LARYNGOPLASTY

Patients may opt for temporary relief of their symptoms, even when eventual recovery is expected. This is accomplished by injection of an absorbable bulking substance into the paralyzed fold to improve the glottic insufficiency. Such substances include various hyaluronic acid preparations, calcium hydroxylapatite paste, micronized human dermis, autologous fat and carboxymethylcellulose-glycerine gel. Factors favouring injection augmentation include:

- dysphagia
- high degree of vocal disability or high vocal demand
- good or indeterminate functional prognosis
- small glottic gap (2 mm to 3 mm)
- no posterior glottic gap
- short life expectancy.

Injection laryngoplasty may be performed via direct laryngoscopy, or perorally or transcutaneously under topical anaesthetic in the office, provided the patient is cooperative and committed. Office use in the awake patient is a major advantage of the technique. Selection of the substance to be injected depends on the surgeon's evaluation of its tissue properties, experience and preference.

Injection augmentation is regarded as temporary since the abandonment of polytetrafluoroethylene polymer (Polytef, Teflon™) because of well-known adverse tissue response. Calcium hydroxylapatite particle paste has been introduced as a durable injectable with effect around one year.

Injection augmentation has inherent limitations. It will not effectively reposition the arytenoid to rectify a height discrepancy or close a posterior glottal gap and is not ideal for large glottic gaps. Most injectates require overinjection to allow for reabsorption, rendering fine adjustment of vocal fold position impossible. In addition, should the injectate infiltrate into an unintended site – typically the superficial layers of the vocal fold, impairing mucosal phonatory vibration – corrective intervention is challenging and patients may have to await natural resolution over weeks to months. It should be noted that no substance today is ideally suited for use in the lamina propria; all currently available substances will stiffen this tissue.

LARYNGEAL FRAMEWORK SURGERY

Framework surgery is generally reserved for treatment of glottic insufficiency from unilateral paralysis that is not expected to improve. Favourable factors are:

- dysphagia
- high degree of vocal disability or vocal demand
- poor functional prognosis
- large glottic gap (2 mm to 3 mm)
- posterior glottic gap
- shortened life expectancy.

In its simplest and most common form, framework surgery consists of medialization thyroplasty, the surgical insertion of an implant, made of silicone, expanded polytetrafluoroethylene (Gore-Tex®), formed calcium hydroxylapatite, or other biologically inert material, into the paraglottic space to displace the paralyzed vocal fold medially (**Figure 78.4**). Typically, this operation is performed under a local anaesthetic, with or without additional intravenous sedation. The surgeon, guided by patient phonation and endoscopic visualization, may thereby size and position the implant for optimal correction of the patient's glottic insufficiency without functional restriction of the airway. The critical anatomic task is to identify the level of the vocal fold in relation to the thyroid lamina, so that the thyroid cartilage aperture through which the implant is inserted can be placed appropriately. Medialization via thyroplasty, in contrast to injection, is precise, predictable and durable. Often considered more aggressive treatment than injection, medialization thyroplasty under local anaesthesia can be safer and better suited to high-risk patients than injection under general anaesthesia.

Serious complications include airway obstruction and perforation into the laryngeal lumen. Necessarily, medialization narrows the airway and, in combination with post-operative oedema and haematoma, can cause airway obstruction. For this reason, some surgeons prefer to observe patients in the hospital for one night following the procedure. Rarely, patients undergoing medialization thyroplasty have been reported to require intubation or tracheotomy in the immediate post-operative period.[36] Perforation of the laryngeal mucosa increases the likelihood of infection and subsequent extrusion of implanted material.

The most common complication, however, is suboptimal voice outcome. This is typically due to technical factors, and revision rates of 5.4% to 14%, to even as high as 33% when adjunctive procedures such as fat injection are included, have been reported.[36–38] Common causes of poor voice result include persistent posterior gap, undermedialization and implant malposition, generally in too anterior or too superior a position (**Figure 78.5**).

Arytenoid repositioning procedures may be added to medialization thyroplasty when there is a poorly supported arytenoid or a posterior gap (**Figures 78.2** and **78.3**). This configuration is difficult to remedy with thyroplasty alone. Arytenoid repositioning surgery is designed to internally rotate and/or suspend the arytenoid in physiologic phonatory position. Most commonly, the muscular process of the arytenoid cartilage is approached through the inferior constrictor muscle and around the back of the thyroid lamina. A non-absorbable suture is passed through this structure and secured to the thyroid lamina to exert anterolateral traction on the muscular process and thus rotate the vocal process medially and slightly caudally. This is known as arytenoid adduction.[39] Adduction arytenoidopexy, a less common approach, involves opening the cricoarytenoid joint capsule and suturing the arytenoid in optimal position directly to the crest of the cricoid.[40]

These procedures are technically more challenging and time-consuming than thyroplasty alone, and have a higher incidence of complications, largely because oedema or bleeding into the paraglottic space can cause airway obstruction. Despite these problems, for the experienced phonosurgeon, arytenoid procedures are an essential adjunct to medialization thyroplasty in achieving an optimal voice outcome.

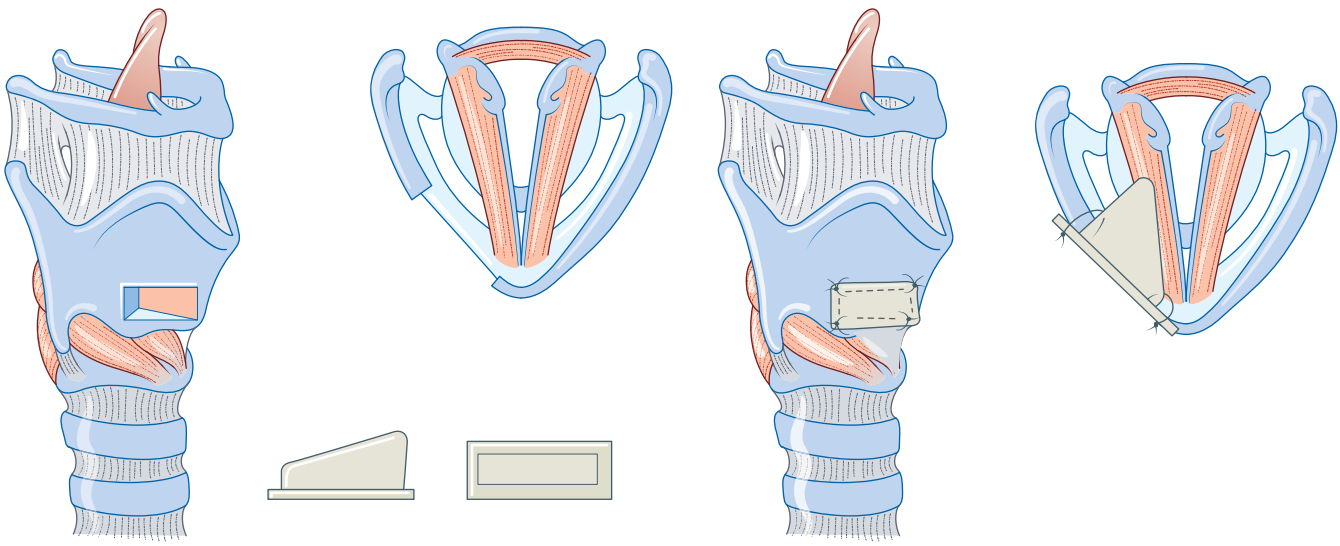

Figure 78.4 In medialization laryngoplasty, a medialization shim of biologically inert material is inserted into the paraglottic space through a thyroid cartilage window to displace the vocal fold towards the midline. Published with permission, from Bielamowicz.[35]

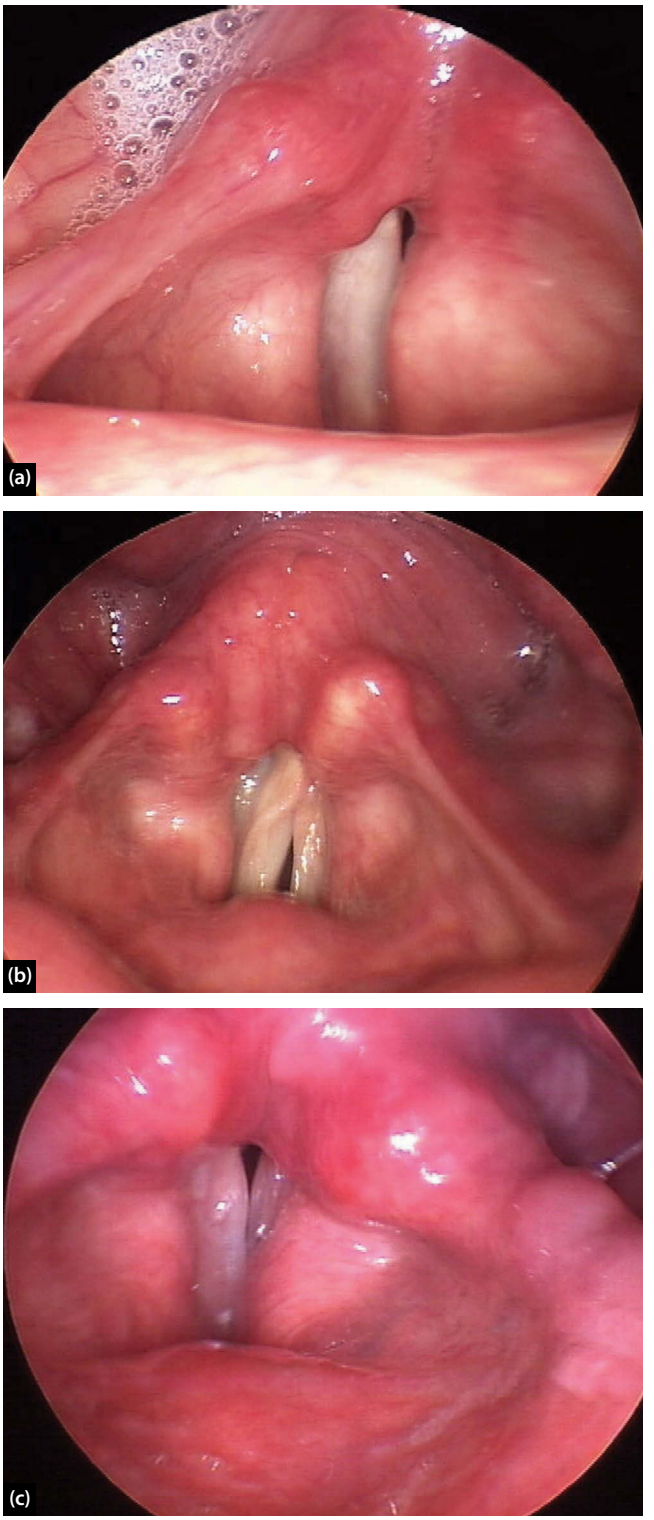

Figure 78.5 Suboptimal outcomes of medialization laryngoplasty. **(a)** Superior implant malposition in this case of left vocal fold paralysis after irradiation of a glomus tumour causes the ventricular fold to obscure the vocal fold, which is not well adducted. This is not supraglottic hyperfunction. **(b)** Inadequate medialization of the left vocal fold in a case of idiopathic paralysis results in persistent midfold glottic insufficiency and compensatory supraglottic hyperfunction. **(c)** Inadequate arytenoid medialization in this case of idiopathic right vocal fold paralysis causes persistent posterior gap. Note supraglottic hyperfunction on the normal (left) side.

RE-INNERVATION

Re-innervation using nearby nerves – both the *ansa cervicalis* and the hypoglossal nerves have been studied[41] – would seem to be an attractive and logical approach to vocal fold paralysis. However, it is subject to the same limitations as spontaneous recovery. Because of the complex innervation of the vocal fold muscles, re-innervation generally stands to improve the bulk and tone of vocal fold muscle but will not restore physiologic motion. Re-innervation is ideally suited when the vocal fold is known to be completely denervated (e.g. if the recurrent nerve or vagus has been sectioned). In fact, in cases of nerve section recognized during surgery, immediate re-anastomosis, or re-innervation if tension-free nerve re-anastomosis is not possible, is the treatment of choice. However, when considering re-innervation later in the course of paralysis, the surgeon should be reasonably confident that he or she is not depriving the vocal fold of existing re-innervation by sectioning a partially recovered recurrent nerve to use the distal stump. The patient must be counselled that symptom improvement may take weeks or months. For this reason, re-innervation has sometimes been combined with other rehabilitation techniques.

BILATERAL VOCAL FOLD PARALYSIS

Virtually any condition that can cause unilateral laryngeal paralysis may affect both recurrent laryngeal nerves to cause bilateral paralysis. Thyroidectomy remains the leading surgical cause;[42] both nerves are also at risk at esophagectomy, tracheal resection, thymectomy and other mediastinal procedures. Similarly, tracheal, esophageal and thyroid malignancies may compromise both nerves. Neurologic disorders tend to cause diffuse involvement of the peripheral nervous system. Amyotrophic lateral sclerosis, post-polio syndrome, Charcot–Marie–Tooth neuropathy, Arnold Chiari malformation and Guillain-Barré syndrome have been documented causes of bilateral paralysis. Some bilateral laryngeal paralyses are idiopathic, attributed to the same infectious agents as unilateral paralysis.

A clinician encountering bilateral vocal fold immobility should consider the possibility of joint fixation or posterior glottic scar, particularly when the condition follows intubation. In such cases the vocal folds are not denervated but merely appear to be, because of mechanical limitation. Careful inspection, sometimes requiring operative laryngoscopy, radiologic investigation and/or electromyography should be used to clarify the diagnosis, as mechanical limitations may be correctible.

Patients with bilateral vocal fold paralysis typically complain of dyspnea, noisy breathing and exercise intolerance. The severity of these respiratory symptoms is inversely proportional to the size of the glottic aperture between the two immobile vocal folds. Respiratory noise is worse on inspiration, as negative pressure pulls the denervated vocal folds into closer approximation. Voice may not be greatly altered, and swallowing is usually not affected.

In acute bilateral vocal fold paralysis, symptoms may be dramatic and even life-threatening. The typical scenario is unexpected respiratory distress after extubation from thyroid surgery and, in such a case, securing an adequate airway is the only consideration. In progressive cases, as found in certain neurologic diseases, patients may compensate as the paralysis becomes denser, and may tolerate unexpectedly small glottic airways. Close questioning about noisy inspiration or limitations in physical activity will suggest that paralysis has been present for some time.

Investigation includes radiologic imaging in the manner of unilateral vocal fold paralysis, with special emphasis on the mediastinum and infra-laryngeal neck, as well as the central nervous system. The degree of airway obstruction may be quantified using a flow-volume loop (see Chapter 76, Laryngeal stenosis in adults). Bilateral paralysis typically shows a variable (rather than fixed) extra-thoracic obstruction, as the vocal folds will passively adduct during inspiration and abduct with positive expiratory air pressure.

Treatment is guided by the degree of airway limitation; except in situations of acute airway distress, the patient may be the best judge of functional handicap. Tracheotomy is frequently performed emergently and may be a reasonable treatment option for the long term as well, as it guarantees airway with minimal compromise of phonation and deglutition. Often, though, patients prefer to avoid the inconveniences of tracheostomy if possible. Other treatment options include lateralization of the vocal fold or removal of arytenoid and/or vocal fold tissue to enlarge the glottic aperture (for more information, see Chapter 76, Laryngeal stenosis in adults). Effort is made to preserve the membranous vocal fold to the greatest extent possible in these procedures, but voice and sometimes swallowing may be adversely affected. Some of these procedures are destructive and irreversible, so the otolaryngologist should be sure that any reasonable possibility of spontaneous improvement has been exhausted before they are considered. Laryngeal pacemakers are currently being evaluated in human trials.[43]

VOCAL FOLD PARESIS

A sophisticated understanding of pathophysiology reveals that vocal fold paralysis is not an all-or-none phenomenon. Paresis, or incomplete paralysis in which some gross vocal fold mobility is preserved, exists alongside complete paralysis as a clinical entity. Symptoms of paresis are predominantly those of glottic insufficiency, even with bilateral involvement. This is because it is rare for paresis to be so dense that it impairs abduction to the extent that the airway is meaningfully narrowed. On the other hand, phonatory glottic function is affected by even mild asymmetries in neural input. Even when glottic closure appears grossly adequate, asymmetries in vocal fold tension may affect pitch, vocal stamina and high or low intensity phonation. Diagnosing paresis may be challenging because preserved gross vocal fold mobility may lull the examiner into overlooking subtle glottic insufficiency or limitations in motion. Perhaps the most difficult task is distinguishing paresis from innocent asymmetries in vocal fold motion, which are probably present in many individuals. Stroboscopy may occasionally be helpful, as subtle decrease in muscular tone affects the amplitude and frequency of the mucosal wave during phonation. LEMG must be used with as much judgement as laryngoscopy, as it probably lacks sensitivity. Because of the diagnostic challenge, there is a role for treatment trials in the form in injection augmentation in patients in whom the diagnosis remains ambiguous.[44]

Most aspects of laryngeal paresis, including prevalence, natural history, laryngoscopic and stroboscopic signs, and relation to other pathology such as mucosal lesions, continue to require clarification.

CONCLUSIONS

Laryngeal paralysis usually results from peripheral nerve injury of one or more laryngeal nerves, and results in clinically significant changes in phonation, swallowing and/or respiration. Often thought of as an all-or-none phenomenon, laryngeal paralysis represents a spectrum of nerve injury and re-innervation, which accounts for the variability in its clinical presentation. Investigation is aimed at discovering underlying causes. Because of the strong laryngeal propensity to re-innervation, paralysis tends to improve over time, and sometimes resolves spontaneously. When it does not, numerous surgical options are available to remedy dysphonia and dysphagia from the glottic insufficiency of unilateral laryngeal paralysis. Respiratory restriction from bilateral paralysis is a greater challenge, however, since most surgical measures are destructive, irreversible and stand to impact voice and swallowing adversely.

FUTURE RESEARCH

- Further identification of factors underlying idiopathic vocal fold paralysis.
- Improved characterization of laryngeal neurophysiology and recurrent laryngeal nerve recovery process.
- Development of reliable quantitative measures in laryngeal electrodiagnostics.
- Development of reliable and stable permanent injectates for definitive office augmentation.
- Dynamic rehabilitation of laryngeal paralysis, including electrical pacing and functional re-innervation.

KEY POINTS

- Vocal fold paralysis can be unilateral or bilateral, either scenario having different clinical implications.
- When facing vocal fold immobility, it is important to distinguish neurogenic paralysis from mechanical fixation.
- Most cases of vocal fold paralysis are caused by peripheral nerve injury.
- Spontaneous nerve recovery is the norm, but not return of function, due to the complex specificities of laryngeal neurophysiology.
- Beyond the treatment of an identifiable cause, management is mainly symptom-driven to address laryngeal dysfunction.
- A wide range of interventions is available to improve most patients' functional deficits.

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CHAPTER 79

OUTPATIENT LARYNGEAL PROCEDURES

Matthew Stephen Broadhurst

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SEARCH STRATEGY

Data in this chapter may be updated by a PubMed search using the keywords: office laryngology, outpatient procedures, laser surgery and transnasal oesophagoscopy.

INTRODUCTION

There have been significant advances in the technology of flexible and rigid video endoscopy, along with innovative techniques that now provide the otolaryngologist with the ability to perform office-based laryngeal procedures. This has enabled surgeons to take the patient from a hospital admission with general anaesthesia and associated risks and downtime, to an office-based setting. Here, the same procedure is performed entirely under local anaesthetic without sedation. With careful patient selection and realistic expectations for outcome, a proportion of the pathology that occurs in the larynx can be well treated in the office through awake unsedated laryngeal surgery (AULS).

Performing AULS provides advantages to both patient and surgeon. The patient can drive themselves to and from the office procedure, can return to work on the same day if necessary and can avoid day hospital admission and general anaesthesia with its inherent risks. In addition, the need to allow diseases such as dysplasia, leukoplakia and papilloma to progress to substantial severity to justify the risks of general anaesthesia is obviated. Instead, patients can undergo a low-risk, simple office angiolytic laser treatment of laryngeal papilloma as an awake procedure in 10–15 minutes with a rapid recovery and minimal downtime. Such office procedures can be performed as frequently as clinically indicated. In addition, in some countries, there is a substantial cost saving for AULS.[1]

It should be stressed that the term 'office-based' and 'outpatient' are often used interchangeably. The critical point is that the patient remains unsedated and is in a totally cooperative state. As such the patient can undergo the procedure either in the surgeon's office or, at times, in the operating theatre.

The more commonly performed laryngeal procedures include laryngeal injection, endoscopic fibre-based laser procedures, transnasal oesophagoscopy (TNO) and panendoscopy, with numerous studies showing adequate patient safety profiles, high patient satisfaction rates and treatment outcomes for laryngeal pathology.[2–6]

HISTORY

The field of laryngology has developed extensively from its inception in the late 1800s. The first laryngology society was formed in the United States and held its inaugural meeting in 1879.[7] Prior to this there had been a tremendous interest in both the anatomy and physiology of voice production and deglutition, with reports of dental mirrors being used to examine the oral cavity as far back as the Roman era. The earliest, most extensive work on the anatomy of voice and hearing, written in CE 1600, came from Julio Casserius.[8, 9] In this text are found eloquent descriptions of the anatomy of both humans and animals. In the mid-19th century, Manuel Garcia,[10] a prominent singer and teacher, perfected mirror laryngoscopy well before it was common practice for

physicians. After rapidly growing fascination in laryngeal anatomy and function, many physicians in the late 19th century became very skilled at mirror examination of the larynx and began to adopt simple procedures that included removal of growths and foreign bodies.[11, 12] In the 1880s, topical anaesthesia with cocaine became available, which greatly aided office laryngeal procedures.[13] At the turn of the 20th century, Chevalier Jackson pioneered the new era of laryngology. It was shortly thereafter, with the use of general anaesthesia and airway cannulation, that laryngology procedures were taken from the physician's office into the operating theatre. In the late 20th century, as technology advanced exponentially, there was a move of laryngology procedures back toward the physician's office as AULS. Today, the modern laryngologist has rigid and flexible high-definition endoscopy and a wide range of rigid and flexible instrumentation to enable safe and effective outpatient laryngeal procedures to be performed.

OUTPATIENT LARYNGEAL PROCEDURES

Table 79.1 lists the various outpatient laryngeal procedures, the more commonly performed being laryngeal injection and endoscopic laser. Injection laryngoplasty is discussed in greater detail in Chapter 67, Phonosurgery and Chapter 78, Paralysis of the larynx. Other less commonly performed procedures include TNO, panendoscopy, removal of foreign bodies, treatment of glottic webs, biopsy and even balloon dilation for stenosis.

Patient preparation

With today's technology affording the ENT surgeon unprecedented abilities to perform both simple and advanced laryngeal procedures in the office or outpatient setting, patient selection and preparation is paramount to minimize risks of cardiorespiratory complications.[14] As with any surgical intervention, establishing a sound rapport with the patient is critical. The ability for a patient to undergo an office-based procedure is greatly enhanced when they have a high comfort level with the treating surgeon and feel confident in his or her care. To this end, informed consent plays a key role in the pre-procedure preparation. A discussion with the patient about the way the procedure is done, the goal(s) of the procedure and the expected and unexpected outcomes are all discussed.

TABLE 79.1 Common outpatient/office-based laryngeal procedures

Laryngeal injection	Injection laryngoplasty	Glottal gap from unilateral vocal fold paralysis, presbyphonia, surgical defect
	Chemical injection	Botulinum toxin, bevacizumab, saline, cidofovir
Laryngeal laser	KTP, PDL, CO_2, Thulium, Gold	Dysplasia, keratosis, papilloma, ectasias, varices, glottic web, granulation tissue, vocal process granuloma
Panendoscopy/ transnasal oesophagoscopy	Diagnostic	Therapeutic

The surgeon must ensure that the patient is a suitable candidate for office-based laryngeal surgery. Contraindications include patients with significant comorbidities, significant airway narrowing, heightened anxiety or extremes of age. For most office laryngeal procedures, patients who are on anticoagulants do not necessarily need to cease them pre-operatively. In the author's experience of over 400 office procedures, there have been 38 procedures performed with patients on anticoagulants (including warfarin). None of these patients have had any bleeding that has been significant, either during or after the procedure.

Local anaesthesia

Inadequate topical anaesthesia for AULS is destined to produce a suboptimal outcome, even despite the surgeon's advanced skill level and highly developed imaging and instrumentation. With this in mind, having a relaxed and well-anaesthetized patient is the critical starting point for successful AULS. The technique for topical anaesthesia will depend on whether the main instrumentation is done transnasally, transorally or transcutaneously.

The most commonly used of all of these is lidocaine due to its rapid onset of action and duration of effect. Although it is relatively low potency in comparison to other local anaesthetic agents, it has an onset of action in as little as 90 seconds and the duration of effect can range from 45 to 60 minutes. With any agent, knowledge of the appropriate dose is critical. The author mainly utilizes 4% lidocaine, representing 40 mg/mL. Toxicity occurs when the dose exceeds 3–5 mg/kg. In an average 70 kg male, the safe dose would be up to 300 mg, equating to 7.5 mL of 4% lidocaine. The maximum volume the author has used in any of the procedures performed has been 4 mL. For most procedures, between 2 mL and 4 mL is adequate to topically anaesthetize the laryngeal mucosa for the range of office procedures to be described.

Lidocaine toxicity must be identified at its earliest signs to enable prompt intervention and treatment. The signs of toxicity include peri-oral and distal upper limb paraesthesia, tinnitus, vertigo, visual disturbance, slurred speech, tremor, tonic-clonic seizures and coma. At the first suspicion of toxicity, the procedure should be halted and emergency management should be commenced.

Patient selection

In the author's experience, approximately 2% of AULS cannot be performed despite adequate preparation. The common reasons for this are intractable gagging despite aggressive local anaesthetic application and severe oropharyngeal crowding. A Friedman Grade 3 or 4 patient[15] can make the procedure difficult and occasionally will need conversion to a transnasal procedure. In some

patients, 10 mg of diazepam can be prescribed if there is a degree of anxiety or heightened gagging, and they will thus have their outpatient laryngeal procedure performed in the operating room.

Patient position

The ideal position for the patient is to be sitting in a typical ENT exam chair that would have them partially flexed forward at the hips. Placing a pillow behind the shoulders can assist in obtaining this position. **Figure 79.1** shows a typical approach for a transoral procedure. The height of the chair can then be raised to suit the surgeon's preference. If a laser procedure is being performed, a small suction catheter is placed transnasally with the distal tip sitting in the oropharynx. The catheter extends across the cheek and is taped securely in place. For any laser procedure the standard laser precautions are observed, which include, but are not limited to, protective eyewear with suitable protection for the wavelength being used and laser-rated surgical mask. Although many procedures can be done as a sole operator without the need of assistance, it is generally advisable to have a nurse, resident, registrar or other assistant at hand.

Transnasal approach

If the procedure is to be done entirely in a transnasal route then simple topical anaesthesia into the nasal cavity and down into the hypopharynx and larynx is sufficient.

Transnasal anaesthesia begins with aerosolized lidocaine mixed with oxymetazoline sprayed into at least one nasal cavity. Techniques often describe spraying both nasal cavities but a careful nasendoscopy prior to the anaesthetic should indicate which nasal cavity is more patent to accommodate the endoscope. In this setting, by only anaesthetizing one nasal cavity, the surgeon can limit the total amount of local anaesthetic used. After waiting the minimum of 3 minutes for adequate anaesthesia and vasoconstriction to take place, the flexible nasendoscope can then be passed, visualizing the entire nasal cavity. As the distal tip nasal endoscope with a working channel is passed into the oropharynx, again careful inspection of all mucosal surfaces takes place. With the endoscope tip sitting approximately level with the tip of the epiglottis, the patient is asked to sustain an 'eee' sound while 2 mL of 4% lidocaine is slowly dripped onto the vibrating larynx. The vibrations disperse the lidocaine to most of the laryngeal mucosal surfaces, providing wide coverage of anaesthesia. At that point the larynx is appropriately anaesthetized and the desired procedure can be performed.

Transoral approach

Due to the superior image quality of rigid transoral endoscopy, most of the author's office procedures utilize a 70 degrees rigid telescope and 1080 p high-definition endoscopy displayed on a 50-inch true high definition plasma monitor. The transoral route is well tolerated in the majority of patients when adequate anaesthesia is administered. The initial delivery of 4% lidocaine is through an atomizing device (**Figure 79.2**) where approximately 0.5 mL is sprayed to cover the tongue base, posterior pharyngeal wall and soft palate. Following this, the tip of the atomizer is angled to 70 degrees (**Figure 79.2** inset) and, with gentle tongue traction, a further 0.5 mL of lidocaine is atomized onto the vallecula, epiglottis and remaining supraglottis. Some lidocaine does contact the glottic surface and into the upper trachea. The endpoint of adequate anaesthesia is when the patient ceases coughing with subsequent topical administrations, keeping in mind the maximal safe volume of 4% lidocaine to use.

Using the rigid telescope in one hand and with either the patient or an assistant providing tongue traction, a curved orotracheal injector is introduced with the other hand. A further 1 mL of 4% lidocaine is slowly dripped onto a vibrating larynx sustaining an 'eee' sound similar to the preparation for transnasal procedures. There is now adequate anaesthesia of the larynx and the planned procedure can be performed. To date, the author has never required more than 4 mL of 4% lidocaine for an AULS.

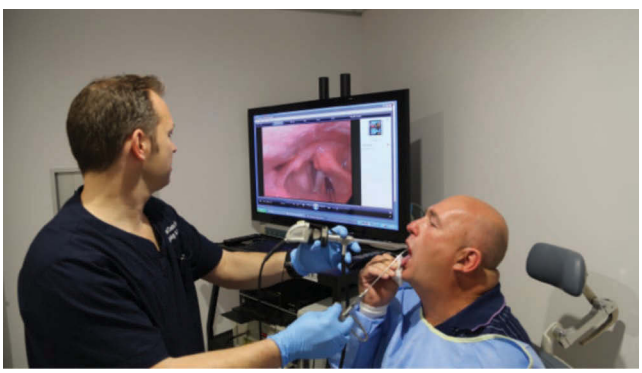

Figure 79.1 The patient sits upright leaning slightly forward flexing at the hips and with slight chin elevation. For the transoral injection laryngoplasty the patient is seen providing traction on their own tongue. This allows the surgeon to use the dominant hand for the injection and the non-dominant hand for the telescope. An assistant is optional, so the procedure can be performed solely by the surgeon.

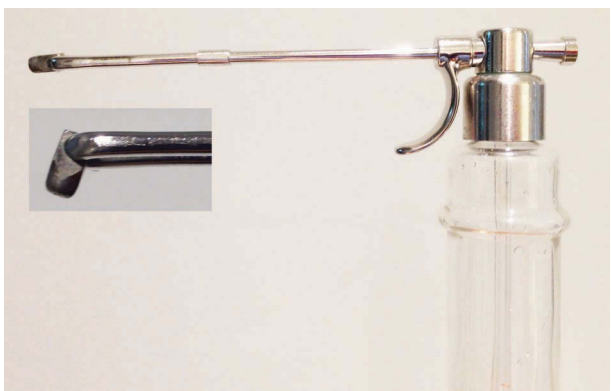

Figure 79.2 An atomizer enables extensive mucosal anaesthesia delivered to the oropharyngeal surfaces. Having graduations marked on the glass bottle can allow a known volume of 4% lidocaine to be used. The inset shows the delivery tip being angled to 70 degrees, which allows excellent mucosal anaesthesia delivery to the hypopharynx, supraglottis and glottis.

Occasionally a bilateral superior laryngeal nerve block is required. The superior laryngeal nerve is found at the midpoint between the superior aspect of the thyroid cartilage and the inferior edge of the hyoid bone laterally. One mL of 4% lidocaine to each side is adequate to achieve sufficient anaesthesia. As with other peripheral-type nerve blocks, approximately 10 minutes is required to have a reasonable effect. Another useful adjunct to topical anaesthesia is administration through a cricothyroid membrane puncture. This universally generates significant coughing and as long as the patient is aware of this pre-injection, they usually find it bearable. The coughing helps distribute the local anaesthetic to benefit the procedure.

LASER LARYNGEAL PROCEDURES

Since the introduction of the carbon dioxide laser into laryngology in the early 1970s,[16, 17] there has been a steady evolution and refinement of the processes for optimizing laser treatment of laryngeal pathology. In the past 15 years there has been an exponential increase in the use of angiolytic lasers in laryngology, both in the operating theatre and in the office. These lasers act by photoablation of the intra-lesional microcirculation through a process termed photothermolysis.[18, 19] Although it has been 30 years since the original description using pulsed dye laser, the modern angiolytic laser industry includes numerous lasers. A list of commonly used office lasers can be seen in **Table 79.2**.

The most commonly used angiolytic laser today in laryngology is the 532 nm potassium titanyl phosphate (KTP) laser. The absorbance of haemoglobin has peaks at approximately 541 nm and 577 nm,[20] allowing the KTP laser energy to be absorbed into the pathology, such as papilloma or dysplasia, with no collateral injury to surrounding normal tissue (**Figure 79.3**). The angiolytic parameters of the KTP laser were studied in the avian chorioallantoic membrane indicating that 35 watts, 15 millisecond pulse width and 2 pulses per second achieved ideal photoablation without surrounding collateral damage. **Figure 79.4a** shows the typical avian chorioallantoic membrane model with its vasculature. **Figure 79.4b** is demonstrating ablation of a single 100 micron vessel without vessel rupture or collateral damage.[20] Findings of this study translated seamlessly to the vocal fold mucosa and remains the author's most frequently used KTP laser settings. In the delicate and highly specialized layered microstructure of the vocal fold, maximal preservation of normal tissue surrounding a lesion is critical to minimizing any vocal deficit.

The 585 nm pulsed dye laser and 980 nm Gold angiolytic laser are less commonly used.[21, 22] All lasers in this class utilize a fibre delivery system, providing the surgeon with a close proximity interface with the laryngeal pathology being treated. Unlike the traditional CO_2 laser through a micro-manipulator using line of sight, fibre delivery office-based angiolytic lasers offer the surgeon safe and effective treatment options for many pathologies encountered. Common lesions suitable for angiolytic laser AULS are listed in **Box 79.1**.

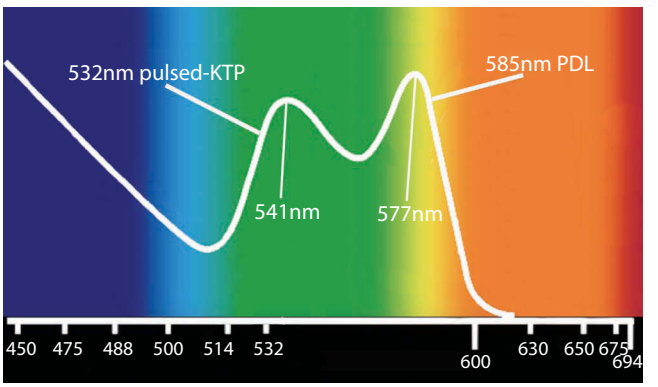

Figure 79.3 The absorbance curve for oxyhaemoglobin shows the peaks of absorbance at 541 nm and 577 nm (thin white lines). Note that the KTP (532 nm) and the pulsed dye (585 nm) angiolytic lasers have wavelengths (thick white lines) in close proximity to the absorbance peaks. This enables maximal absorption of laser energy into the microcirculation of the pathology resulting in photothermolysis.

TABLE 79.2 Angiolysis/fibre-based lasers in comparison

Laser	Wavelength	Chromophore	Advantages	Disadvantages	Fibre size (microns)
KTP laser	532 nm	Haemoglobin	• Haemostatic pulsed and continuous cuts similar to CO_2 • Low cost	• None	300–600
Pulsed dye laser	585 nm	Haemoglobin	• Haemostatic	• Dye kit unreliable	600
Gold laser	980 nm	Haemoglobin	• Haemostatic	• Limited data	300
Thulium laser	2010 nm	Water	• Haemostatic • Smallest fibre	• Increased heat	260–600
CO_2 laser	10600 nm	Water	• Clean cutting	• Increased heat • Large fibre • Cost • Non haemostatic	1210

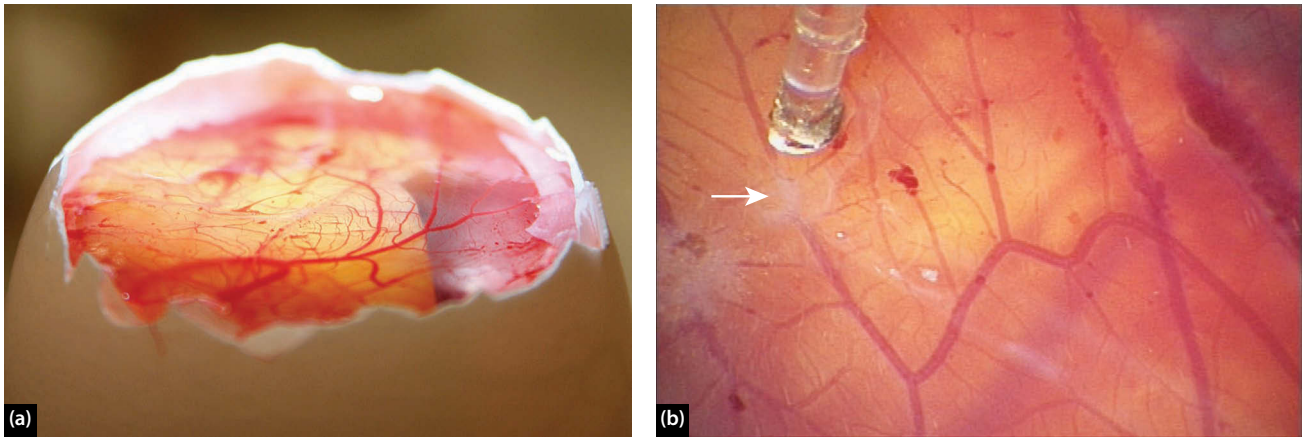

Figure 79.4 The chorioallantoic membrane of a leghorn chicken has been exposed in a day 9 fertilized egg and shown in (a). It provides an established model for simulating vocal fold angiolysis. **(b)** demonstrates the ablation of a second order vessel with no collateral damage to the albumin. The KTP laser was used with a 300 micron fibre, 35 watts, 15 millisecond pulse width and 2 pulses per second.

BOX 79.1 Laryngeal pathology suitable for treatment by awake unsedated laryngeal surgery (AULS)

- Dysplasia
- Keratosis
- Papilloma
- Ectasias
- Varices
- Granulation tissue
- Vocal process granuloma
- Polyp

As the target chromophore is haemoglobin, angiolytic lasers are extremely haemostatic and selected patients can be treated without ceasing anticoagulants. This can significantly simplify management of some patients who may be on warfarin and have laryngeal papillomatosis requiring multiple treatments per year. In contrast, traditional management includes repeated microlaryngoscopies under general anaesthesia, often using the microdebrider or cold steel and therefore necessitating cessation of antiocoagulant therapy. Although not in the angiolytic class, the CO_2 laser can now be used through a fibre delivery system.[23, 24] The BeamPath™ ENT fibre (Omni-guide, Cambridge, Massachusetts, USA) has a spot size of 320 microns but the outer diameter is quite bulky at 1.21 mm. When placing a fibre in the working channel of a flexible endoscope, smaller fibres (such as 300 microns for KTP laser) enable more efficient suctions around them than a larger fibre such as the Omniguide (**Figure 79.5**). Another non-angiolytic fibre-based laser is the 2010 nm thulium laser (Revolix Jr, Lisa Laser, Pleasanton, California, USA). With the chromophore being water, it is highly versatile and haemostatic although it does produce somewhat more heat than the KTP laser.[25–27] The thulium laser has the smallest available fibre, being 260 microns, and has benefits over the CO_2 laser in reduced cost for the laser unit, smaller fibre diameter and – being a solid-state laser – is markedly more reliable (see **Table 79.2**).

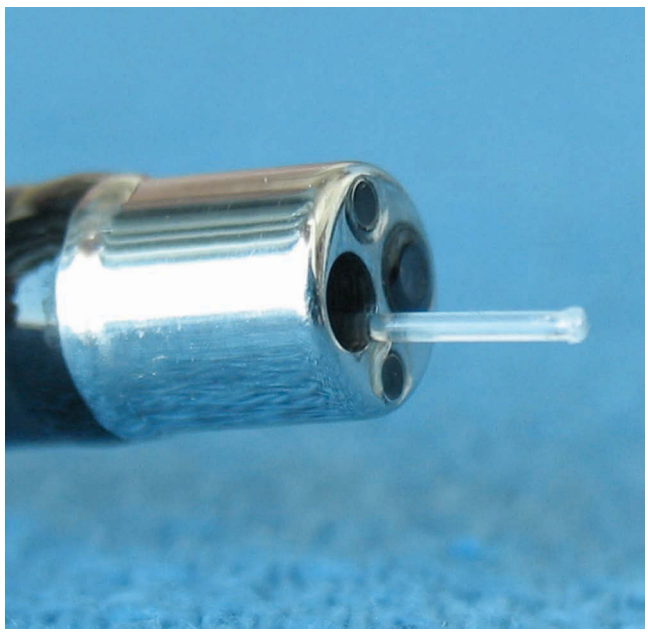

Figure 79.5 The smallest fibre appropriate should be used as this maximized the available space within the working channel of the endoscope for suction. Musocal secretions can become quite viscous and the less space occupied by the fibre in the working channel, the better. A 300 micron KTP laser fibre is seen protruding from the distal chip endoscope with significant suction space around the fibre.

LARYNGEAL PATHOLOGY SUITABLE FOR AWAKE UNSEDATED LASER LARYNGEAL SURGERY

Laryngeal pathology with prominent microcirculation can be well treated in the awake unsedated patient with fibre-based laser systems. (**Figure 79.6** and **Box 79.1**)

Laryngeal dysplasia

Many patients with field change to the glottic mucosal surfaces require careful and frequent office review to monitor

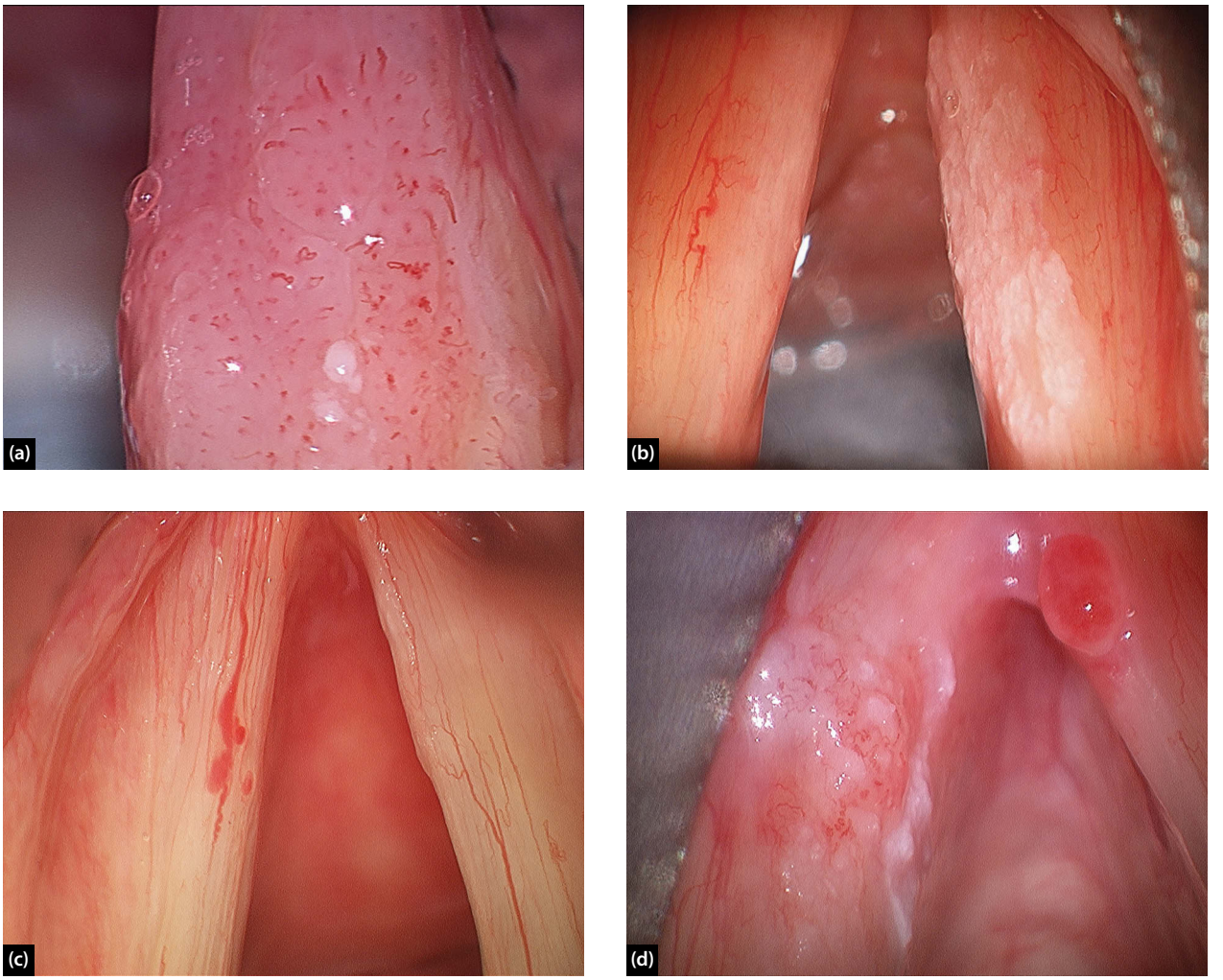

Figure 79.6 Angiolytic lasers are particularly effective for AULS due to the prominent microcirculation within some laryngeal pathology. Laryngeal papillomatosis in **(a)** demonstrates the aberrant angiogenic pattern. **(b)** shows left vocal fold ectasias with right vocal fold dysplasia. A varix and ectatic vessels are seen in a professional opera soprano in **(c)**. A small T1a squamous cell carcinoma in **(d)** further highlights the aberrant vessel growth pattern with these lesions. In all pathologies depicted, the angiolytic laser energy is absorbed by the microcirculation leading to lesion ablation with maximal preservation of the surrounding layered microstructure of the true vocal fold.

the extent of the dysplasia and keratosis and for possible malignant transformation. With the high resolution of endoscopy and fibre-based laser systems, many of these patients can now be managed with AULS procedures. In this setting, angiolytic laser ablation of regions of keratosis or dysplasia is performed and small biopsies can be taken. The procedure is generally very well tolerated and avoids the frequent hospital admission, general anaesthesia and multiple biopsies with traditional management. This in turn avoids the risks of permanent voice impairment and repeated general anaesthesia. The angiolytic epithelial ablation allows for subsequent re-epithelialization of the laryngeal mucosa tending to normalize this layer. Such a result can be seen in **Figure 79.7a** and **79.7b**. A typical glottic mucosal picture is seen with keratosis and dysplasia (**Figure 79.7a**). After a single office KTP laser ablation and more than 2 years following the procedure, the vocal folds still appear normal (**Figure 79.7b**) and the voice remains markedly improved. The concept of proactive management in field change keratosis/dysplasia is a substantial step forward in managing this difficult condition. It moves the surgeon away from the traditional 'wait and see' approach, where periodic microlaryngoscopies under general anaesthesia with biopsies cumulatively destroy the voice in managing benign disease. Benefits of this paradigm shift include preservation of the voice by avoiding multiple glottic biopsies and reduced burden on the outpatient clinics as close follow-up of field change is no longer applicable.

Laryngeal papillomatosis

Patients with laryngeal papillomatosis are well known to require multiple hospital admissions under general anaesthesia to manage this condition. The goals of treatment are to maintain airway patency and for voice preservation. It must be stressed that papilloma arises from the epithelium and as such, treatment should be confined to a depth

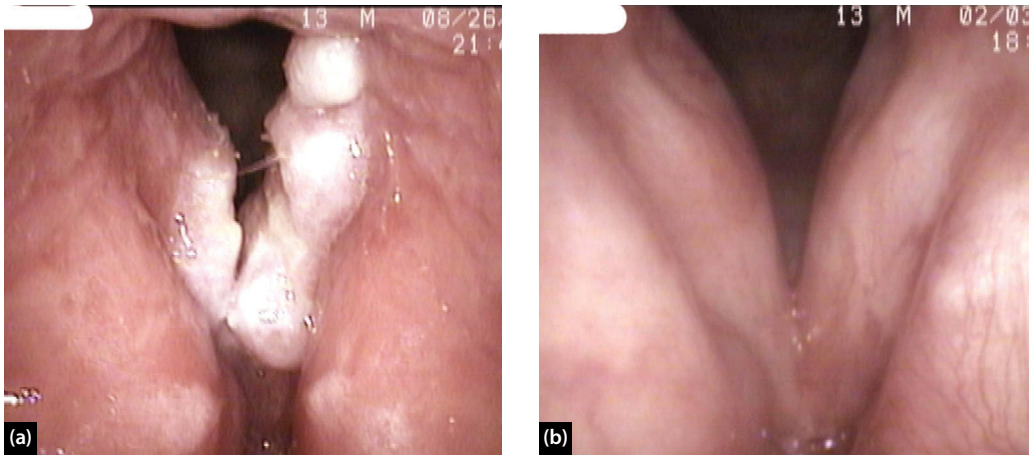

Figure 79.7 A typical patient with extensive keratosis and dysplasia is depicted in (a). This patient was medically unfit for general anaesthetic and was initially offered curative intent radiation for a presumed glottic cancer by the multidisciplinary team. He was then treated by the author with AULS utilizing KTP laser. Biopsies showed dysplasia but no cancer and after two office treatments the entire glottic surfaces normalized as, did his voice with follow-up now at 3 years **(b)**. This is a typical outcome for such a patient and avoided unnecessary radiation.

no more than the epithelial layer. Under traditional management the patient typically undergoes repeated general anaesthaesia and use of the microdebrider or non-angiolytic lasers to control the disease. To limit the number of general anaesthetics, procedures tend to be scheduled before there is substantial regrowth. In this setting, with the loss of many landmarks, it is not difficult to stray deep to the epithelial layer of the vocal folds and permanently denude the superficial lamina propria (SLP). As this can occur over many treatments with time, many patients become vocal cripples. As a paradigm shift, these patients can be initially controlled in theatre with angiolytic lasers and then transferred to the office setting for maintenance treatment with angiolytic lasers.[28, 29] Performing office procedures to control laryngeal papillomatosis can also limit the risks associated with frequent general anaesthesia and airway surgery.

In a typical initial presentation in a patient with extensive disease, treatment is first undertaken at microlaryngoscopy in theatre with general anaesthetic. In this setting, the author uses KTP laser ablation of all laryngeal papillomatosis. It is critical under the operating microscope to identify all mucosal areas of papilloma and treat them. For very early disease, the most subtle finding for papilloma is loss of the linear blood vessel growth pattern in normal mucosal. One can clearly see the loss of this normal pattern in **Figure 79.8** as the epithelium thickens and the vessels become aberrant with papilloma growth. Once this visual sign is noted, the surgeon can quickly identify areas of abnormal epithelium both under the operating microscope and using office-based high definition endoscopy. In both settings, angiolytic laser ablation can then be carefully directed to the diseased surfaces. With the appreciation of the subtle vascular changes seen clearly under high definition office endoscopy, there is little need for additional expensive endoscopy devices such as narrow band imaging.

At microlaryngoscopy, careful inspection of the ventricles is critical. On numerous occasions in tertiary referral cases, the author has found papilloma filling the ventricles that had not been noted at the referring ENT centre. In a setting such as this, seen in **Figure 79.9**, endoscopic removal of the false cords exteriorizes the ventricles and allows for both subsequent surveillance and treatment of recurrent papillomatosis. Having adequate access to all laryngeal mucosal surfaces is invaluable in the office-based setting to manage recurrent laryngeal papillomatosis.

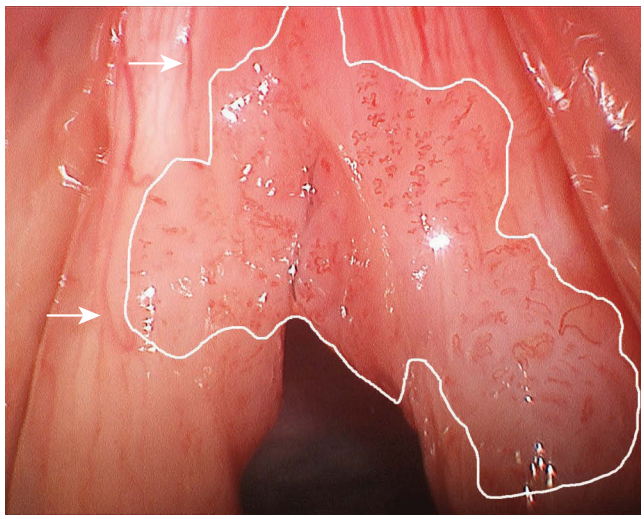

Figure 79.8 The loss of normal linear vascularity of the true vocal fold mucosa is seen clearly, outlined in white, by papilloma growth. The mucosa thickens and aberrant angiogenesis leads to the typical papilloma appearance, which can be clearly defined from the surrounding normal tissue. Being acutely aware of this interface appearance can allow the astute surgeon to easily identify abnormal regions of papilloma in the office setting and deliver target-specific angiolysis.

After office-based angiolytic ablation of the papillomatosis, subepithelial tissues are injected with bevacizumab.[30,31] Bevacizumab (Avastin®), a vascular endothelial growth factor inhibitor, appears to reduce the angiogenesis critical to papilloma regrowth, and can reduce the frequency of procedures and extent of papilloma recurrence. In some patients, the disease has remained in remission.[32]

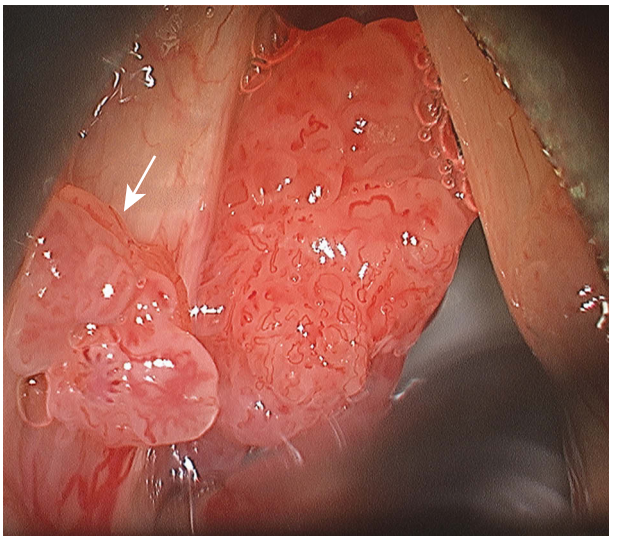

Figure 79.9 It is crucial in managing papilloma to closely inspect each ventricle at the time of microlaryngoscopy. This allows clearance of the entire ventricular disease, such as that shown by the white arrow. The false cord is also removed exteriorizing the ventricle. This enables unobscured surveillance of all laryngeal mucosal surfaces and enables easy access to the ventricle should disease recur.

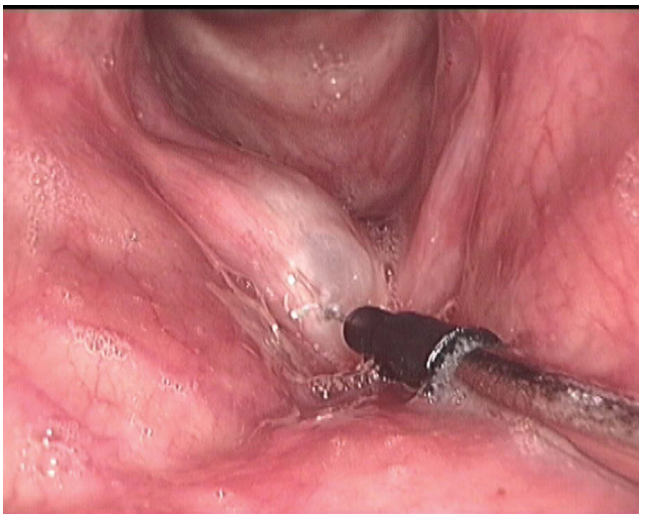

Figure 79.10 A simple office-based injection into the superficial lamina propria (SLP) can be performed as adjunctive treatment to angiolytic laser ablation of laryngeal papilloma. Note the distention of the SLP from the bevacizumab injection at 25 mg in 1 mL. This 10-minute awake procedure greatly simplifies managing some laryngeal conditions avoiding repeated microlaryngoscopies.

The half-life for bevacizumab is approximately 1 month. Given this, office-based injections are likely to be most effective when the supposed angiogenic 'switch' occurs within that month. **Figure 79.10** shows a typical injection in the office setting of bevacizumab, avoiding the need for general anaesthetic for such a short and simple procedure.

Patients with more aggressive or frequent recurrences tend to respond better to bevacizumab injections. Doses typically used are 25–50 mg (25 mg/ml).[30–32] Since first using Avastin in 2009, the author has noted many patients to have total eradication of the disease, who prior to commencement on bevacizumab, underwent multiple procedures per year. The only change associated with the eradication of papilloma has been the addition of KTP laser and bevacizumab to the management.

Laryngeal ectasias and varices

Some patients may present with a small vascular anomaly of the vocal fold and the only treatment necessary is removal of the lesion. For a simple ectasia or varix that is causing recurrent haemorrhage in a professional voice user, ablation of the lesion is required. Although this is typically done in the operating theatre under general anaesthesia with microlaryngoscopy, in suitable patients where there is no additional underlying pathology (e.g. nodules) the surgeon can ablate the lesion in the office setting safely with an angiolytic laser with maximal preservation of the layered microstructure of the true vocal folds.[21, 28, 33–35]

Figure 79.11 shows a typical lesion in a 62-year-old male causing recurrent haemorrhage. It was easily ablated with the KTP laser (settings: 35 watts, 15 ms pulse width, 2 pulses per second) as an awake unsedated office procedure with no recurrence at 1-year follow-up.

Arytenoid granuloma, laryngeal granulation, polyps and glottic web

There are numerous other entities that can be treated in the awake unsedated patient. This can be an attractive alternative when risks of general anaesthesia to the patient are high or there is patient preference for avoiding general anaesthesia or hospital admission. The lack of precision in treating these entities during an awake procedure when compared to suspension microlaryngoscopy and general anaesthesia needs to be explained to the patient.[36, 37] However, treating an arytenoid granuloma, polyp or granulation is a debulking procedure and high level precision is not critical. In polyp management, reports indicate reduction in size can be achieved with office laser treatment. Mallur et al. reported all lesions to have regressed over a 1-year follow-up.[38] Ivey et al. reported that office pulsed dye laser was able to reduce the polyp size by greater than 70% in approximately one-third of cases. It was also reported that up to 40% of patients did proceed to phonomicrosurgical resection as definitive treatment.[36] Although polyps can be debulked in this setting, it is more in the patient's best interest to elect for a near 100% success rate by treating a vocal fold polyp in theatre with microlaryngoscopy utilizing phonomicrosurgical techniques rather than accepting a simple reduction in lesion size through an office debulking procedure, which can sometimes involve multiple procedures.

Techniques for awake unsedated laser laryngeal surgery

As discussed under the injection section, the approach for laser treatments in the awake unsedated patient can be either transnasal or transoral. The author's laser preference is the

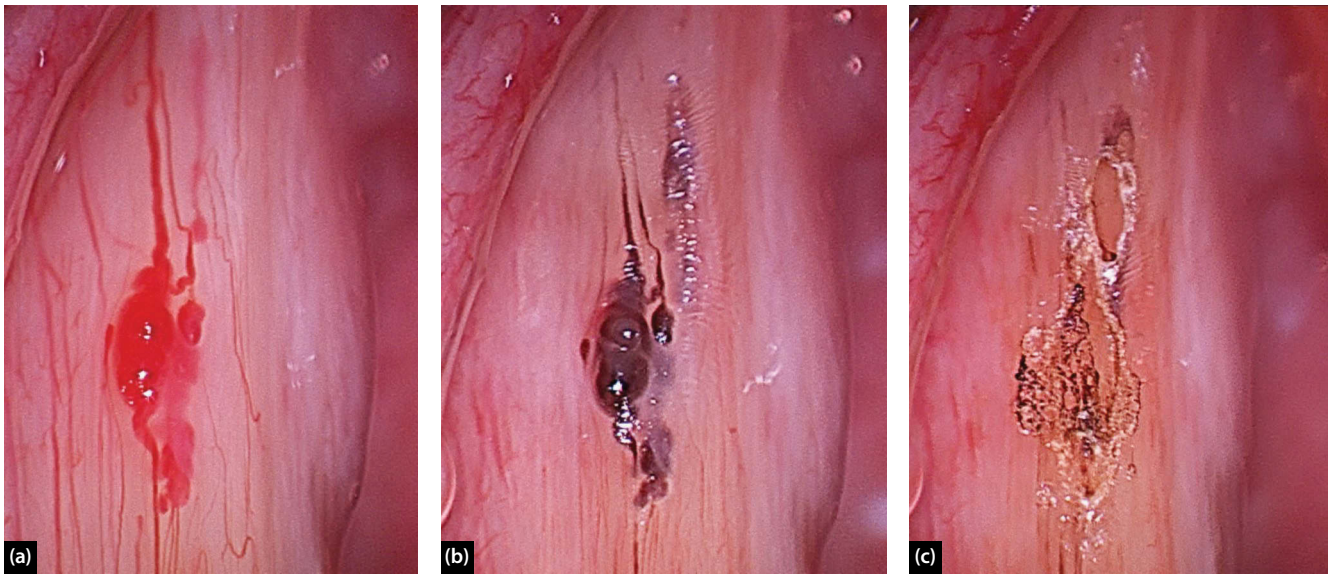

Figure 79.11 A 62-year-old male with recurrent true vocal fold haemorrhage from a large left vocal fold varix. (a) This can be easily ablated with an angiolytic laser (KTP laser in this case). Note the coagulum formed before final ablation **(b)** and no collateral injury to the true vocal fold layered microstructure **(c)**. After 1 week of voice rest, review showed complete resolution and at 2 years there remains no recurrence.

532 nm KTP laser (Aura XP, American Medical Systems, Minnetonka, MN) due to its small fibre size (300 microns), solid state, relative portability, variable power, pulse width and pulse frequency, and reasonable price.

In the transnasal approach, the patient preparation and distal chip flexible endoscopy placement is identical. For simple lesion ablation such as papilloma or ectasias, the fibre is brought into view and the laser is engaged. Initial blanching of the lesion will occur before it is completely ablated. **Figure 79.12** shows the glottic papilloma being ablated with the KTP laser. After the lesions blanch and are suctioned free, the underlying surface heals cleanly. If papilloma is being treated, then after ablation, the fibre tip or endoscope tip can be used to dislodge treated disease. After this, the under surface can be inspected and treated if necessary. Although lidocaine can have a 45–60 minute duration of anaesthesia, only approximately 15 minutes of adequate anaesthesia time for an awake procedure is available. Despite this, the majority of papillomatosis in a patient's larynx can be successfully treated in one setting, while occasionally a staged procedure is required for extensive disease.

For an arytenoid granuloma, granulation tissue or a polyp, the laser fibre is held in contact mode and the lesion ablated. Suction or the tip of the scope can be used to manually debulk the lesion further as treatment is completed. **Figure 79.13** shows the treatment of a vocal process granuloma with KTP laser and botulinum toxin injection in the office setting. The procedure took 10 minutes and the patient was able to drive himself home shortly after (**Figure 79.13**). These lesions can also be treated using the CO_2 or thulium lasers with fibre-based delivery. Both are highly efficient at removing such tissue and the latter is highly haemostatic. If using these lasers, care must be taken not to overtreat the base of the lesion at its interface with any SLP. These lasers have a markedly higher likelihood of creating thermal damage to the underlying SLP with subsequent fibrosis and scarring resulting in dysphonia.

TRANSNASAL OESOPHAGOSCOPY, PANENDOSCOPY AND BALLOON DILATION

ENT surgeons have long been competent in rigid oesophagoscopy and bronchoscopy in the theatre setting under general anaesthetic. In the office setting, hundreds of times each year, ENT surgeons use flexible nasopharyngoscopes to assess the upper airway. With improvements in distal chip image quality and narrow endoscopes with a working channel, the surgeon can progress forward to a more comprehensive aerodigestive tract assessment. Building on the highly familiar nasopharyngoscopy technique, the ENT surgeon can now pass the endoscope safely into the oesophagus and trachea for close-proximity assessment and treatment.

TNO is increasingly being used by otolaryngologists, with the advantage of avoiding hospital admission and sedation, which is traditionally performed in endoscopy suites. Although TNO can be performed with a bronchoscope, dedicated endoscopes are available for the purpose. The outer diameter ranges from 3.1 mm to 5.3 mm. A port or working channel is required (2 mm diameter) for suction, biopsy forceps, injection device or a laser fibre. An alternative model is to use a sheath around the endoscope that incorporates insufflation and instrumentation channels. The advantage of the sheath technique is that the endoscope does not need to go through a full sterilization cycle and several patients can be assessed in a single setting.

Common indications for TNO (listed in **Box 79.2**) include laryngopharyngeal reflux, dysphagia, monitoring

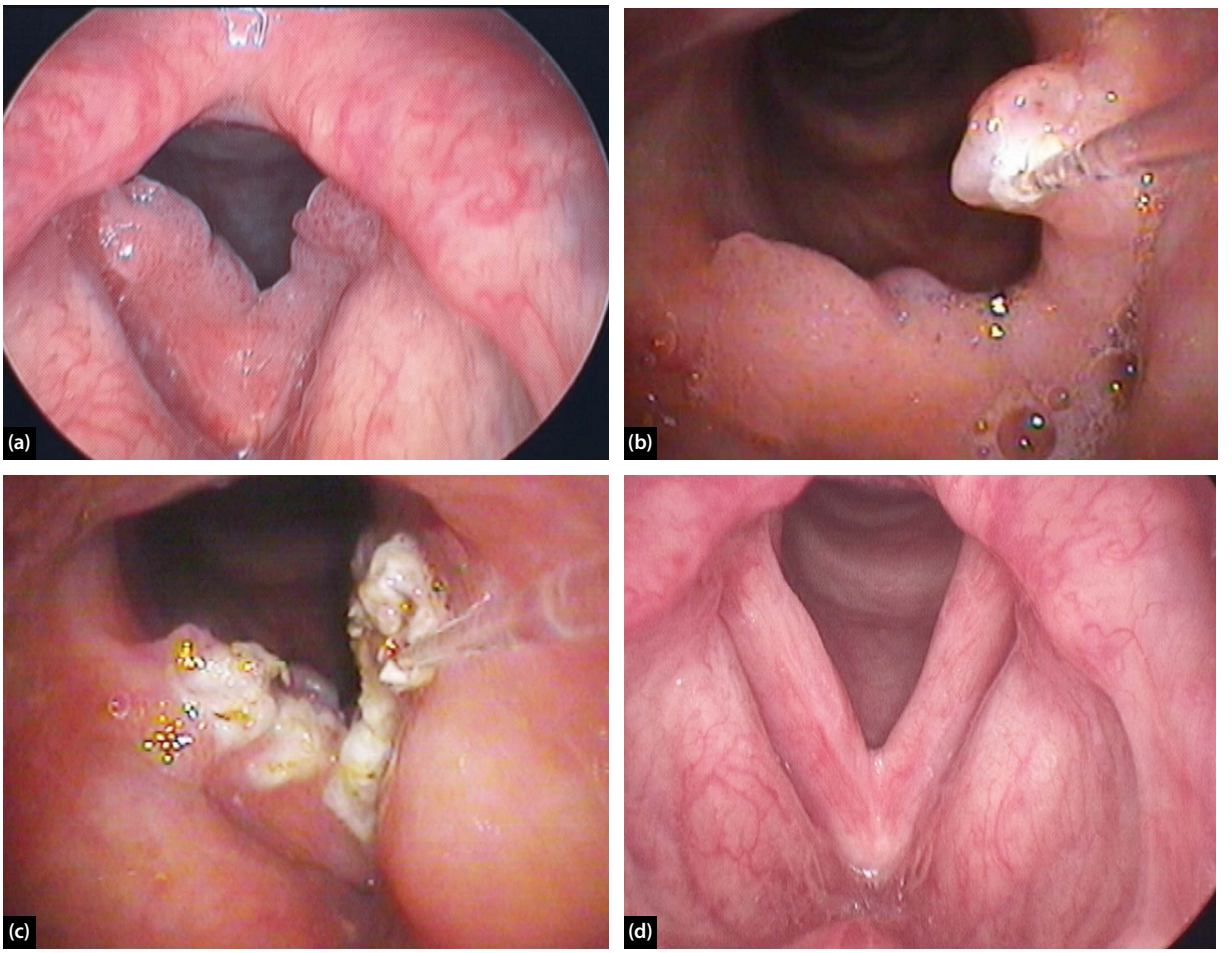

Figure 79.12 Typical glottic papilloma is seen covering both vocal fold surfaces in (a). Initial ablation with a 300 micron KTP laser fibre (settings: 35 watts, 15 ms pulse width, 2 pulses per second) of the posterior left papilloma is seen in **(b)**. As the procedure continues, **(c)** shows the majority of the papilloma is now ablated and can be scraped free with the fibre tip or the endoscope tip. After two office treatments and 2 years later, the patient remains free from papilloma **(d)** and with markedly improved voice. This patient had undergone previous microlaryngeal surgery with severe anaesthetic reactions. He refused microlaryngeal surgery offered prior to his referral to the author but agreed to AULS. Note the absence of any bleeding in the procedure due to the significant haemostatic nature of the KTP laser.

of Barrett's oesophagus, screening for head and neck cancer, chronic cough and procedural (injection Botox, balloon dilation, tracheo-oesophageal puncture and placement of pH probes). It is important to note that, in skilled hands, there is no measurable difference in diagnostic accuracy rates between conventional oesophagoscopy and the newer TNE.[6, 38–45] In addition, for TNO the patient tolerance is very high and risks are minimal. Rates of epistaxis are below 2% with vasovagal events being even less common.

Aside from TNO, the same endoscope can be used to perform panendoscopy in the office setting,[45] although routine bronchoscopic evaluations are not performed these days owing to the availability of high resolution CT scans. In a primary workup, for example of a small vocal fold tumour, a 15-minute in-office panendoscopy can safely provide the necessary information. Traditionally, a head and neck cancer patient would undergo a hospital admission, general anaesthesia with biopsy and panendoscopy (microlaryngoscopy, oesophagoscopy and bronchoscopy) for assessment of the disease extent. In selected patients this can be safely done in the awake unsedated patient in the office. Utilizing AULS, equivalent information is gained when compared to the traditional panendoscopy but it does spare the patient the downtime of a hospital day/overnight admission and the general anaesthetic. This is particularly attractive to patients who may be returning in a week or two for definitive surgery and minimizes their time in the hospital system and number of procedures. If a biopsy is required, in selected patients this can be done with a cup forceps through the channel of the endoscope or with a transoral approach using curved biopsy forceps, seen in **Figure 79.14**.

Reports have emerged of in-office balloon dilation for upper tracheal or subglottic stenosis.[46, 47] Although there appears to be reasonable safety, temporarily occluding a patient's airway in the office must be cautioned against. This can be simply performed in theatre and dramatically reduce patient risks. Achker et al. reported on a subglottic stenosis treated under general anaesthetic in which the balloon catheter failed to fully deflate. The catheter, while under traction maintaining the balloon in the desired location, tore and left a partially deflated balloon lodged in the trachea. Fortunately, during the general anaesthetic the balloon could

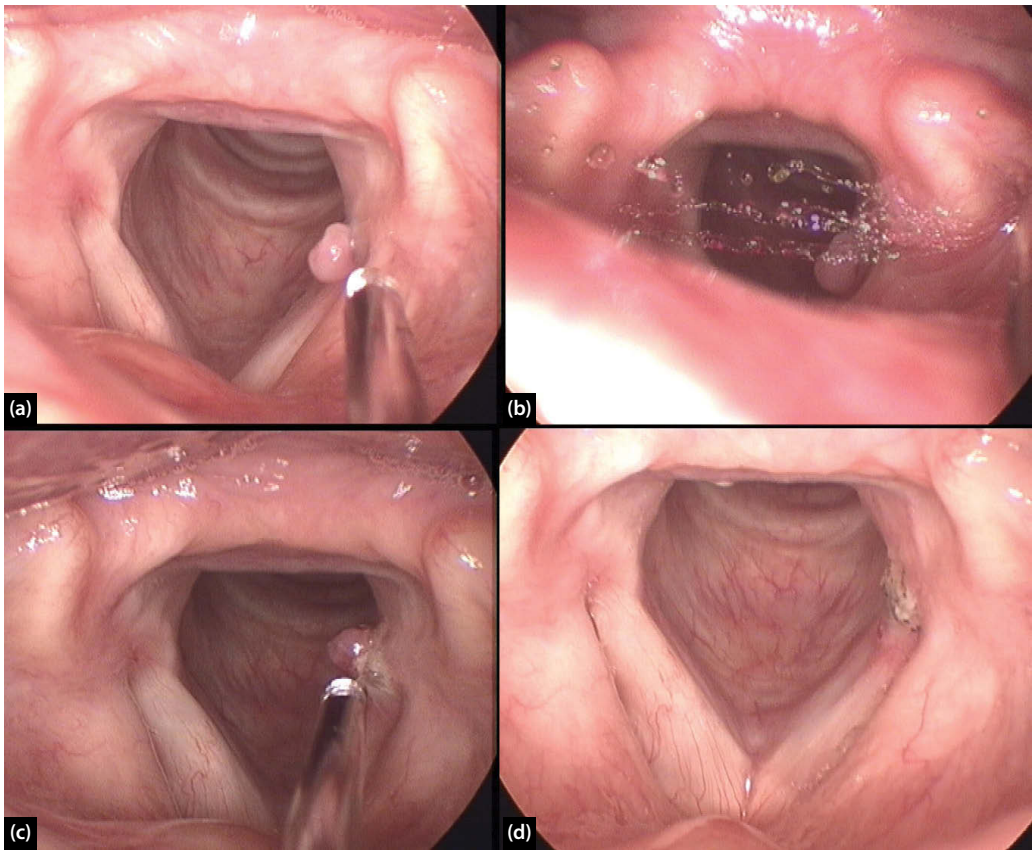

Figure 79.13 Although not routinely required in the author's practice, debulking of an arytenoid granuloma can be performed with AULS. **(a)** shows the left arytenoid granuloma; **(b)** demonstrates the dripping of 4% lidocaine for topical anaesthesia; **(c)** shows the KTP laser fibre delivered transorally through an oro-tracheal injector to ablate/debulk the lesion; **(d)** highlights the minimal collateral thermal injury by angiolytic lasers and the patient then underwent botulinum toxin injection into each thyroarytenoid and lateral cricoarytenoid muscle as part of the procedure. There was total resolution of the lesion by 1 month and he has remained granuloma-free for over 2 years.

BOX 79.2 Indications for transnasal oesophagoscopy (TNO)

- Diagnostic:
  - dysphagia, globus, laryngopharyngeal reflux
  - monitoring Barrett's oesophagitis
  - head and neck cancer surveillance
  - panendoscopy + biopsy
- Therapeutic:
  - balloon dilation
  - angiolytic laser therapy
  - tracheo-oesophageal puncture
  - botulinum toxin injection
  - foreign body disimpaction

be fully deflated and removed with no adverse patient outcome. If that occurred in the office setting, patient death would have been the likely consequence.[48]

Patient preparation and position

Patient position and topical anaesthesia for TNE or panendoscopy is identical to that described for transnasal laser or injection procedures. In addition, however, the patient is asked to be nil by mouth for 3 hours pre-procedure. The distal chip endoscope is passed into the nasal cavity and advanced to the hypopharynx, inspecting all mucosal surfaces on the way. The patient is then asked to lean with chin forward and down, as if looking over a fence, while the endoscope tip is advanced into the pyriform fossa. At this point, the patient is asked to swallow and gentle caudal pressure on the endoscope will allow it to pass into the upper oesophagus. Air insufflation is then used to dilate the oesophageal lumen and mucosal inspection is carried out as the endoscope moves caudally into the stomach.

There are three anatomical narrowings in the oesophagus that should be anticipated:

1. Aortic arch, at 26 cm, identified by pulsations on the left anterolateral wall
2. The left mainstem bronchus, which can be seen on the anterior wall at approximately 2 cm below the aortic arch
3. The lower oesophageal sphincter at the distal oesophagus.

After inspection of the stomach and retro-flexion to view the gastro-oesophageal junction and antrum, the scope is retracted. Further inspection occurs with withdrawal of the scope, noting the squamo-columnar junction. The endoscope can then be passed through the anaesthetized

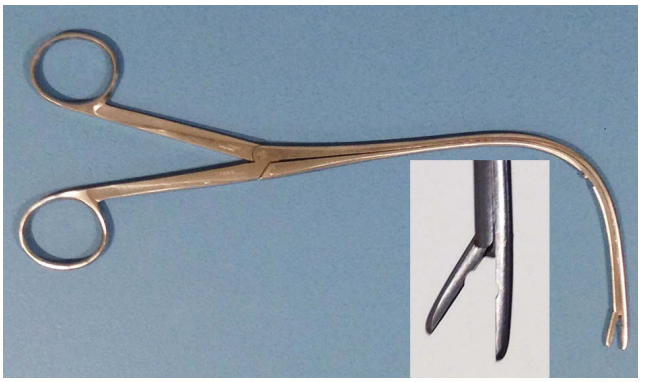

Figure 79.14 During a panendoscopy a lesion can safely biopsied in selected patients with a transoral biopsy cup forceps as shown. Note the cup jaws in the inset that enable a generous biopsy to be taken under direct vision.

vocal folds to inspect the subglottis, trachea and main stem bronchi. Following this procedure, the patient remains nil by mouth for 1 hour to minimize aspiration.

SUMMARY

With significant improvements in endoscopic technology and instrumentation of the upper airway there has been an exponential increase in AULS performed in the operating theatre or office setting. Although the majority is performed in the office, reimbursements can drive patients to the operating theatre for AULS.

Injection of a wide array of substances can be safely and reliably performed in patients in the office setting, managing a range of pathologies including vocal fold paralysis, presbyphonia, glottic defects from cancer resection, botulinum toxin, bevacizumab and saline. Angiolytic lasers (commonly the KTP laser) delivered by small flexible fibres can be used to treat a vast range of laryngeal pathology and obviate the need for hospital admission and general anaesthetic in selected patients. Patient selection and preparation, together with realistic expectations for the surgical outcome, are critical in utilizing this newly established approach to patient management.

KEY POINTS

- With improvements in technology, significant experience has accumulated worldwide in outpatient laryngology.
- This skillset is especially valuable in managing patients who may be unsuitable for general anaesthetic assessment of the larynx (poor general health or anatomical reasons that hamper access).
- A variety of basic and advanced laryngeal interventions can be performed in the outpatient setting (biopsy, cord injection for medialization, botulinum toxin injection and laser surgery.
- A robust emerging body of evidence supports incorporating transnasal oesophagoscopy into ENT practice, a procedure that has also found favour among gastroenterologists.
- The transnasal oesophagoscope can also be used for interventions such as tracheoscopy and oesophageal dilatations.

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Section 2
Plastic Surgery

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CHAPTER
80

RHINOPLASTY FOLLOWING NASAL TRAUMA

Charles East

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SEARCH STRATEGY

Data in this chapter may be updated a Medline search using the keywords: rhinoplasty, trauma, saddle nose deformity, deviated nose nasal septal reconstruction, nasal valve.

INTRODUCTION

Nasal fractures are the commonest facial fracture and occur at all ages. Forty per cent of facial fractures affect the nasal bones, and many of these involve damage to the nasal septum. It must be remembered that external forces sufficient to create a bony or cartilaginous deformity also damage the overlying skin and soft-tissue envelope, commonly leading to a scar or contour abnormality.

Both functional and aesthetic problems occurring after injury may prompt a patient who might not otherwise consider operations to seek treatment and the variation and variety of defects require a very extensive knowledge of septal and rhinoplasty surgery to correct these deformities adequately.[1]

A distinction should also be made between childhood and adult fractures, as any injury in the growing nose will likely have consequences for future nasal development. Growth in the facial skeleton is more often than not asymmetric and may result in the appearance of a 'damaged nose' even when there is no history of prior significant trauma.[2] Trauma, however, can be superimposed on pre-existing deformities or in a patient who has had a previous rhinoplasty such that the patient attributes the whole deformity to an injury, so it is essential to enquire about pre-injury status functionally and aesthetically – if possible with old photographs.

ASSESSMENT

It should be clearly documented whether the primary issue is functional, aesthetic or both. In addition to the standard clinical rhinoplasty photographs, a head-down photograph is very useful in determining displacement or deviation of the normal dorsal aesthetic lines. Each third of the nose should be examined, looking for irregularity, asymmetry or deviation. In the basal view, particular attention should be paid to the caudal septum, nostril symmetry and any insufficiency of the nasal sidewall.[3] There is often valve dysfunction following trauma and particular attention needs to be paid to each of the four plains of the nasal valve, both medially and laterally. Endoscopy is very useful in evaluating the dynamic status of the nasal airway in both the natural and decongested mucosa and particularly to assess any turbinate hypertrophy.

Treatment of acute nasal injuries frequently results in persistent asymmetry or deformity, often necessitating secondary reconstructive surgery. Lateral blows to the nose may produce a simple, depressed nasal bone, displacement of the bony/cartilaginous pyramid or deviation of the nasal axis in the lower two-thirds due to vertical fracture of the cartilaginous septum. Frontal blows may produce a simple fracture of the tip of the nasal bones, injury to the cartilaginous vault with widening of the bridge and, in more severe injury, horizontal fracture or fractures of the septum leading to loss of height either in the middle third or at the anterior septal angle. This is the

TABLE 80.1 Possible residual deformities following nasal trauma

Area of nasal trauma	Possible residual deformity			
Upper third	Depression of bridge – central or unilateral	Lateral displacement	Asymmetric lateral displacement	Vertical displacement of bone(s)
Middle third	Upper lateral cartilage collapse – loss of septal height	Lateral displacement with septal dorsal line	Asymmetric displacement	
Lower third	Loss of projection (septal angles) Dome asymmetry, bossa	Collapse of nostril margin, deviation of tip, caudal septal dislocation	Soft-tissue loss/ scar- notching irregularity	Lengthening of upper lip, acute columella/ labial angle
Skin envelope	Scar, tattooing, contour loss			
Nasal valve dysfunction	Septum angulation Septal loss, perforation	Lateral nasal sidewall insufficiency	Synechiae	

saddle nose deformity. **Table 80.1** illustrates the various types of residual deformity following trauma.

TIMING OF SURGERY

Primary management of trauma

The window to reduce a nasal fracture is variable but most advocate closed reduction within 2–3 weeks, possibly earlier in children. Early reduction is indicated for upper-third bone deformities and this may range from simple elevation of a depressed bone to a four-step manoeuvre in an impacted deviated pyramid. Here, the deformity is exaggerated using a Walsham type forceps to disimpact the vertically placed bone further outwards, the opposite (depressed) bone is then lifted out away from the deviated side, before a straight Ash forceps lifts the central vault of the pyramid including the upper septum and moves it back to the midline before manually pushing the sidewalls inwards to close the roof. Unstable pyramids should have an external splint applied for a week and an internal splint if concomitant disimpaction of the septum is required via a submucosal approach.[4]

Post-trauma rhinoplasty can be undertaken in the acute or subacute period or at an interval following the main injury. The main indication for early rhinoplasty (open reduction of nasal fracture) is for treatment of an acute saddle deformity to reconstruct septal height or in complex nasoethmoidal fractures where the nasal bones need to be stabilized (see Volume 1, Chapter 107, Nasal and facial fractures). Rhinoplasty techniques applicable in the acute phase are those usually to restore the height of the dorsum from a frontal blow such as falling forwards against an edge. In this scenario, as well as the nasal bone widening, there is collapse of the septum under the upper laterals. This is difficult to restore at a later date once scarring and fibrosis are established.[5] Fixation of the dorsal keystone area may be required using drill holes in the thicker part of the nasal bones and suture fixation to hold the perpendicular plate/quadrilateral cartilage together, with repair to the upper laterals (**Figure 80.1**) A supporting piece of posterior perpendicular plate with perforations or cartilage may need to be sewn to support the fragments of the lower two-thirds of the septum.

Lacerations to the skin over a compound fracture need to be closed primarily but may provide access enabling primary reduction of displaced nasal bones. In general, reconstructive rhinoplasty apart from manipulations is usually deferred until the soft-tissue envelope has healed.

'The missed opportunity' – sub acute

Where the nasal bony pyramid is displaced but the time from injury has passed that of closed manipulation, reopening the fracture lines usually with a 2 mm osteotome endonasally or via stab percutaneous approach can remobilize the fragments and allow better realignment. In this instance classical osteotomies are not performed, only those that reopen the partially healed fractures. If there is a history of pre-trauma deformity, then adequate realignment is unlikely, and it is probably wiser to counsel the patient to let the fractures and the skin envelope settle and consider a formal rhinoplasty after 6 months.

POST-TRAUMA RHINOPLASTY

General principles

This covers soft-tissue envelope damage, acquired nasal deviations, sidewall deformity/asymmetry, dorsolateral contours and the nasal septum.

The key structure to repair is the septum, especially when there are high septal deviations such as occur in Chevallet fractures, loss of the septal angles or where there has been septal cartilage necrosis due to haematoma. The important principle is to create a stable dorsal line connected to the nasal bones and then correct the position of the anterior and posterior angles as these two important points determine the support of the tip cartilages, nostril shape and the columella–labial profile. Being the least supported part of the nose, the caudal/dorsal free septum is the most frequently damaged. Simple oblique fractures can be released and the fragments secured by batons or pieces of perforated

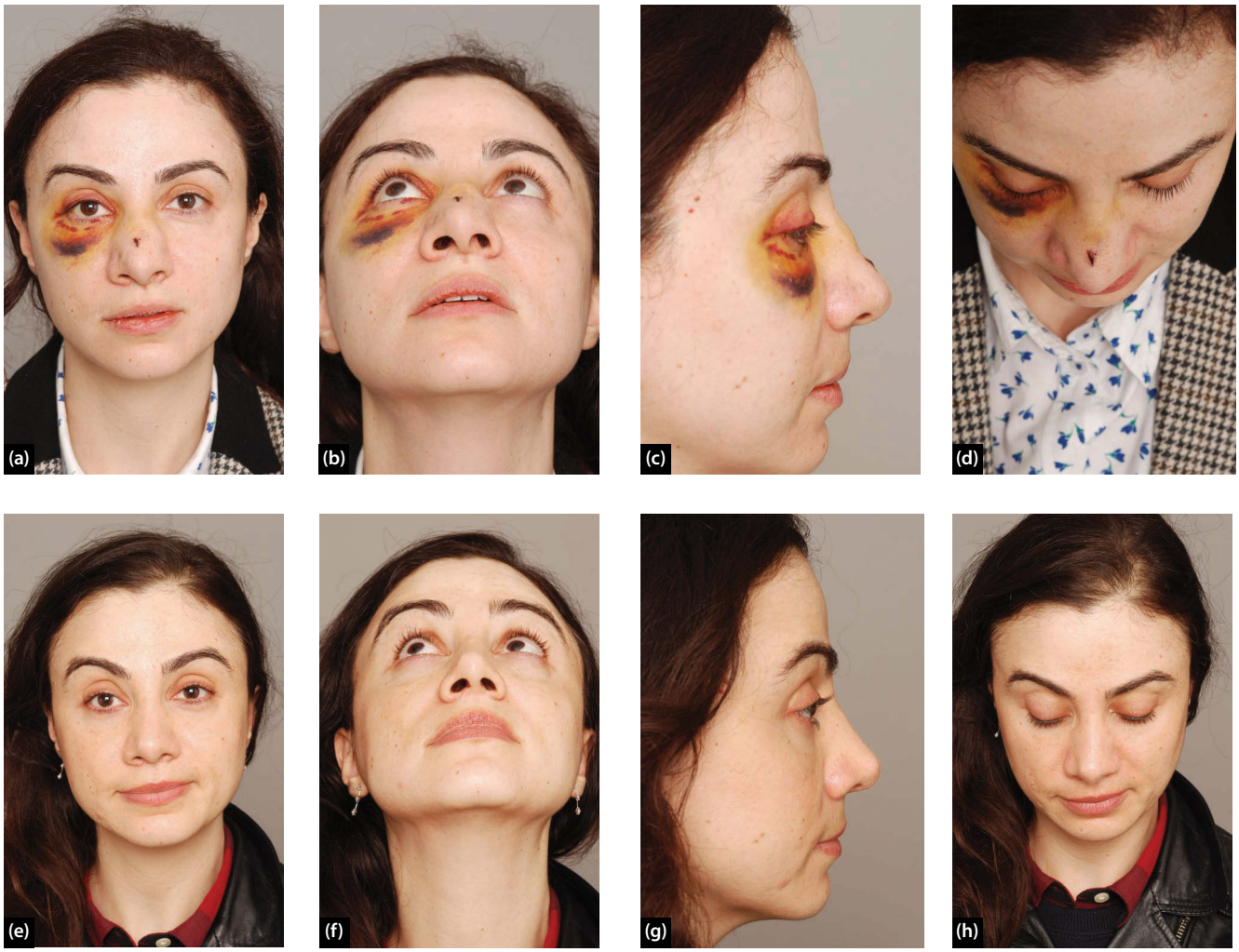

Figure 80.1 (a–d) Acute saddle nose deformity following a frontal blow to the mid dorsum. **(e–h)** Post treatment.

perpendicular plate sutured usually on the more concave side. Curvature of the leading edge of the dorsum will usually require reinforcement: bilateral spreader grafts (often asymmetric) provide a secure compression that is not always possible with a unilateral graft.[3]

If the deformity is severe and the cartilage scarred or of poor quality, it is better to replace the dorsal or caudal septum. Invariably, wide exposure via the external approach with full septal dissection gives the best control to evaluate the deformity and to reconstruct. A graft, either from more posteriorly in the septum or from costal cartilage, is required (and spreader grafts are also needed to stabilize the dorsal line), so an adequate source of durable material is required. Rib cartilage can be difficult to use and choosing the more horizontal sixth or seventh rib via a medial inframammary approach gives a straighter graft. Grafts should be thin, and the most effective way to reduce warping is to laminate two pieces that have opposite curvature.[6] This technique produces a stable, straight construct that in the long term minimizes the risks of deformity. Another technique is obliquely sectioning the rib cartilage to include cortex and medulla, thereby having a balanced graft,[7] although this may not produce adequate lengths for extended spreader grafts.

The most important fixation point is to the nasal spine, which should be midline. If not, the spine may need to be modified and a specific drill hole should be made for firm suture fixation, not relying on periosteal attachments. The dorsal and posterior quadrilateral cartilage needs to be secured to the residual dorsal septum or affixed to the perpendicular plate and nasal bones. The reader is referred to the references for further reading.[8] Where the existing frame is unusable, a new L-shaped strut has to be created, usually as two or three individual cartilages pieces cut to lock together and fixed with PDS sutures. This gives the option to extend the caudal septum forward to act as a 'tongue in groove' with relatively rigid fixation for the medial crura and will correct columellar retraction. Alternatively, a septal extension graft fixed between two extended spreader grafts and sutured to the caudal septum will achieve the same objective. The leading edge, however, must be in the midline.[9]

Upper third

Modern appreciation of dorsal anatomy recognizes that there is a nasal bone cap covering the upper lateral cartilage/septal cartilages with an average of 7–8 mm,[10] so deformities in the upper third invariably involve cartilage as well as bone. Common deformities include a depressed fracture of one bone with attached upper lateral, depression of one bone with fracture of the upper septum and overriding of the contralateral bone, or a lean of the whole osseocartilaginous vault away from the midline. Fracture of the tip of both bones with loss of height of the underlying septum creates a middle vault saddle with a 'pseudo hump' above. These deformities can be very difficult to correct by traditional osteotomies and need a different approach with more controlled sculpting of the bones by fine rasps or, better, by modern power tools or Piezo surgery.[11]

Creating predictable fractures with osteotomes is difficult because old fracture lines reopen and comminution of bones can occur. Pre-operative CT facial bone scanning with 3D reconstruction allows more accurate planning. If the nasal bone sidewalls are straight, an open–close book osteotomy sequence including the central upper bony septum will realign the nasal sidewalls, the excess height being reduced from the oblique bone as it is orientated more vertically.[12]

With irregular thickness or shape of the nasal bones, rather than comminution, resculpting with Piezo or a power tool to create better bone shape, changing convexity and permitting a controlled movement minimizes the risk of residual irregularity. The use of securing sutures through the bone and upper septum allows a more satisfactory repositioning than leaving flail segments with little control of how they heal.[13] This requires a different approach from what has been practised since the time of Jaques Joseph of multiple comminuting osteotomies and prolonged splinting, internally and externally.

Contrary to previous teaching, the whole soft-tissue envelope can be raised from maxilla face to maxilla face. Collapse or loss of the nasal bone does not occur when the internal periosteal lining is preserved and this is a significant advantage in using the Piezo device, which will not damage soft tissue. It is not advisable to perform such a wide dissection, however, if traditional osteotomes are used as the internal lining support cannot be guaranteed.

Final contouring of defects or concavities can be done with autologous tissue, such as diced cartilage, either free like a paste, with a fascia wrap (diced cartilage wrapped in fascia – DCF)[13] or moulded using a physiological glue (e.g. platelet-rich fibrin).[14] The use of shavings of cartilage for small volume contours is well established and there is evidence of improved survival of these grafts using them together with platelet-rich fibrin.

Because of the relationship with the cartilage of the mid third, cranially extended spreader grafts between the nasal bones may be used as the solid foundation to widen a narrow upper third over which a more flexible graft can be placed to give a smooth contour.

Middle third

The middle-third support is important to the function of the nose as this is part of the complex area of the nasal valve. A depressed fracture of the nasal bone laterally with the attached upper lateral, internal synechiae across the valve angle, weak vertically placed upper laterals, high septal deviations, loss of height of the septum at its attachment to the upper lateral or damage at the scroll area will all impact on the valve function. Indeed, it is often easier to reconstruct the mid-third contour aesthetically with spreader grafts than to establish a normal functioning valve from collapse.

The lateral middle third is one area that needs to be tensioned between the attachments at the pyriform aperture and the dorsum to prevent dynamic collapse. The principle after adequate septal repair is to support the junctional roof, which is naturally vaulted cranially and caudally presents an angle said to be about 10–15 degrees. Spreader grafts are the mainstay of treatment here for the damaged nose and can be placed at the same level as the septum, just below to act as a pedestal to allow tensioning of the upper lateral sidewall or above the septum if an increase in height is needed and the septum is not being replaced. They are usually asymmetric in size to allow correct contouring of the neodorsum. In the approach to conservation and reorientation, if one upper lateral is large, it may be folded to be used as a turn-in flap (spreader flap), particularly on the oblique side of a deviated nose. Addition to the mid third by onlay grafts to produce the correct contour may also be considered.

Nasal tip/lower third

Fracture, buckling or loss of cartilage can produce multiple deformities in the tip, commonly with associated soft-tissue damage. Through and through scars in the envelope or previous areas of skin loss pose particular challenges in trying to create a smooth contour, especially when involving the rim. It is helpful to consider the dorsal septum/anterior angle position with the tip cartilages as this is the foundation for any repair. Loss of tissue volume usually requires reconstruction with grafts; the ear is a good source as appropriate curved pieces of cartilage either alone or as composite grafts with skin can be tailored. Defects in otherwise healthy tissue up to 2 cm can be composite grafted successfully. With an undamaged envelope, tip repair can be achieved by endonasal techniques if only one area needs attention, but with a more complex problem, especially when the septum is to be reconstructed, the open approach permits wide exposure, release of contractions and accurate repair or grafting.

Commonly used grafts of cartilage are strut grafts between the medial crura, shield and cap grafts, rim grafts for nostril sidewall stability and lateral crural grafts, either to augment or to replace a lost framework.[15] For details of repair of the nasal skin envelope, the reader is referred to Chapter 85, Nasal reconstruction.

The damaged nasal valve

The nasal valve is the flow-limiting segment of the upper airway and has an important function in directing airflow to the middle nasal meatus, as well as providing eddies of air for antegrade olfaction. Interference of the normal airflow may result from damage to the lining with synechiae, and insufficiency of the nasal sidewall either with a fixed deformity at the pyriform or a dynamically unstable sidewall. The addition of active rhinitis or the compensatory hypertrophy of the turbinates either inferior or middle needs to be considered. There are also the medially based deformities related to the nasal septum and the conjoined upper laterals.

The surgical goals need to be defined by identifying the specific areas of deformity medially, laterally, at the vaulted roof and occasionally the sill of the nose. CT scanning with modelling of the valve can assist in planning but assessment by direct vision endoscopically remains the usual examination.

The accuracy needed to maintain the correct septal height and width as well as maintaining the roof/sidewall stability cannot be overemphasized. Often the difference between success and failure is a millimetre in this complex zone, and it is important with any graft not to lose in bulk what you gain in strength.

Whichever method is chosen to repair the wall, it is the author's belief that a customized intranasal splint is essential in the first week, particularly if a three-layer dissection has been undertaken (i.e. skin, cartilage and vestibular lining having been released in the lower two-thirds of the nasal sidewall).

The skin envelope

The variable thickness of the envelope is considerable in the nose. Probably the most frequently traumatized area is at the rhinion where the skin is thinnest. Lacerations, stellate splits and grazing injuries should be cleaned and dressed primarily to prevent tattooing. Subsequent scars and loss of the subcutaneous tissue may fix the skin to the framework of the nose. If this is a risk, massage of the skin using moisturizer will help once the skin has healed. Adequate sun protection of scars and use of silicone gel daily all contribute to good cosmetic scar result. In thin, damaged skin and severe subcutaneous tissue loss, fat grafting to the nose will improve the contour and in atrophic skin add stem cells to improve the quality. This may be considered before definitive repair of the nose using fine cannulae.

Camouflaging the dorsum skeleton at the time of surgery in the presence of thin skin may be achieved by using autologous temporalis fascia, perichondrium from rib or rectus abdominis fascia. Both of these provide a uniform sheet to thicken the envelope and are easier to prepare than periosteum from the retroauricular area. If used over large areas, it is important to suture the sheet with fine absorbable sutures. This type of graft is particularly useful to cover reconstructed cartilage domes in the nasal tip.

REVISION SURGERY

Surgery for the traumatized nose by definition involves repair of damaged tissue. Predictability of outcome should be discussed with the patient, particularly where complex grafting is undertaken as there is a greater need for further, usually minor, revision. This is particularly so when dealing with both functional and aesthetic issues and it is wise to discuss this before any repair.

Infection is a major cause for creating a poor result through loss of tissue, so careful pre-operative evaluation including microbiology culture of the vestibule to exclude MRSA and appropriate advice on post-operative care are considered essential.

Common causes for revision may involve nasal valve disorders (e.g. thinning a wide rib graft caudal septal reconstruction), resuspending a sidewall collapse or a contour problem (e.g. minor saddling, especially at the central keystone area). As with all rhinoplasty revisions, if the skin envelope needs to be fully raised, an interval of about a year is advised. Singe-area deformities can be revised earlier dependent on the skin quality and extent of the area to be augmented/reduced. Alar base correction may be undertaken safely at an early point after the major repair.

NASAL TRAUMA AND CHILDREN

It is recommended that children with trauma requiring reconstruction are referred to specialist centres as often orthognathic and orthodontic services are required parallelling nasal repair.

Children's nasal injuries are common and have the potential to disrupt normal growth, particularly with loss of septal cartilage, as happens with a septal abscess.

Oblique fractures usually heal with fibrous union so continued growth will often produce a deviation from the rhinion. In general it is best to defer surgery at least until after puberty and as close to maturity as possible. This deformity increases with age and it can be difficult to resist pressure to operate early before nasal maturity. The timing is variable between sexes and in individuals and requires a judgement of skeletal maturity and mental maturity in planning the repair, but in general the repair should be as close to skeletal maturity as possible. Osteotomies do not disturb growth of the nose but damage to the growth centres in the septal cartilage does.[16] The septodorsal cartilage and the sphenospinal cartilage should not be disturbed, but conservative relocation on the spine or release of an angulation may be necessary.[17] The patient's parents need to be warned of a possible second operation when growth has stopped.

Where a saddle occurs, replacement by autologous cartilage is preferred as continued growth may then occur. Expansion of the skin envelope by serial placement of Custom silastic dorsal implants replaced every 18–24 months will prevent the problems of the short nose with a tight envelope and allow a definitive correction later, usually employing rib cartilage.

BEST CLINICAL PRACTICE

- ✓ Nasal trauma is a complex issue needing specialist assessment.
- ✓ Childhood injuries need to be monitored to assess growth.
- ✓ Early reduction and alignment of fractured nasal bones with or without septal release should be carried out within 2-3 weeks and acute saddles require early surgical intervention to restore septal height.
- ✓ Cartilage depleted noses will usually need rib grafts for reconstruction and the basis for a stable nose with good breathing is a reconstructed septum and a properly tensioned sidewall.
- ✓ Secondary procedures are common in repair of damaged noses. Finally the soft tissue envelope may also need augmentation.

KEY POINTS

- A suitable referral pathway needs to be established for early assessment of nasal trauma.
- Nasal endoscopy and cone beam CT scanning are helpful in assessment and planning repair.
- External approaches and grafting techniques are usually required.
- Patients should be consented for all graft harvest sites.
- Regenerative surgical techniques may enhance graft survival and improve the quality of damaged skin

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CHAPTER 81

PRE-OPERATIVE ASSESSMENT FOR RHINOPLASTY

Hesham Saleh and Catherine Rennie

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SEARCH STRATEGY

Data in this chapter may be updated by a PubMed search using the keywords: facial proportions, facial, aesthetics, nasal, examination, assessment and rhinoplasty.

INTRODUCTION

Rhinoplasty is one of the most challenging procedures in facial plastic surgery and consideration must be given to both facial aesthetics and nasal function. It is technically difficult to achieve consistently excellent results and, as the surgery is on the most prominent part of the face, the aesthetic outcome is visible to all. Meticulous planning is therefore essential.

This chapter outlines a systematic approach to the assessment of patients for rhinoplasty/septorhinoplasty that will enable appropriate patient selection and facilitate surgical planning. Assessment should include:

- consideration of the patient's motivations, anxieties and expectations
- analysis of the face
- analysis of the nose
- examination
- photography.

THE PATIENT

It is essential to obtain a clear history of the patient's complaint and symptoms. Identification of any structural, congenital, traumatic, cosmetic and/or functional issues is crucial. Any past history of nasal surgery, sinonasal disease, diabetes, psychopathology, anticoagulant medication, smoking or cocaine use should be elicited.

It is critical to understand the patient's motivations, anxieties and expectations. Why is a patient prepared to undergo the risk and inconvenience of an operation to correct often seemingly minor deformities? Many people have nasal abnormalities but would not consider surgery, so what makes a patient choose to have surgery? For many rhinoplasty patients, their focus on their nose stems back to puberty and daily reflection in the mirror leads to increasing dissatisfaction in their appearance.[1] Studies have shown higher levels of dissatisfaction in personal appearance in patients seeking rhinoplasty than those seeking other aesthetic procedures.[2, 3] In the majority of rhinoplasty patients the motivation for surgery comes from a desire to change or from witnessing favourable outcomes in others.[4] For most it is not the severity of their deformity that leads them to surgery[5] but their perceived difference from the norm in their social environment. The timing for rhinoplasty often coincides with a loss in self-esteem. Rhinoplasty has been shown to have a positive effect on the patient's body image, which is found 3 months post procedure and is still evident 2 years following the procedure.[6]

Identifying high-risk patients

It is important that surgeons recognize potentially problematic patients, as high-risk patients are unlikely to be satisfied with surgical results. A number of unsuitable personality attributes have been described in the literature. Examples commonly referred to are patients with body dysmorphic disorder (BDD), those who are unreasonably demanding or overly flattering, patients who insist on secrecy, the so-called surgiholic, as well as obsessive, perfectionist and impolite patients. The simplified acronyms SIMON (single, immature, male, overly expectant/obsessive, narcissistic) and SYLVIA (secure, young, listens, verbal, intelligent, attractive) describe some of characteristics of the high-risk and the ideal patient respectively.[7–9]

Body dysmorphic disorder

BDD describes an altered perception of one's own appearance that results in distress. It is a subjective feeling of ugliness or physical defect which the patient feels is noticeable to others, although the appearance is within normal limits.[10] Its occurrence is summarized in **Box 81.1**.

The onset of BDD is typically in late adolescence; it is a chronic rather than episodic condition and affects both genders equally. Picavet et al found that 33% of patients seeking rhinoplasty had moderate symptoms of BDD. Only 2% of those seeking rhinoplasty for a medical reason had BDD whereas 43% of those seeking rhinoplasty for purely cosmetic reasons had BDD.[12]

Three questions to ask patients, based on the DSM-IV criteria, have been developed to help surgeons screen for BDD:

1. Are you worried about your appearance in any way?
2. Does this concern or preoccupy you? That is, do you think about it a lot and wish you could worry about it less?
3. What effect has this preoccupation with your appearance had on your life?[13, 14]

A number of both specific and generic questionnaires are available that can help identify patients with BDD (**Box 81.2**). These are designed to be used with those patients with behaviours suggesting BDD. Particular 'red flags' are shown in **Box 81.3**.

BOX 81.1 Body dysmorphic disorder: by the numbers[11]

BDD occurs in approximately:

1%	Adult population
2.3–13%	Students
13%	Psychiatric patients
14–42%	Outpatients with atypical major depression
11–12%	Outpatients with social phobia
39%	Inpatients with anorexia nervosa
6–20%	Patients seeking cosmetic surgery

BOX 81.2 General and specific questionnaires and questions for patients

Specific questionnaires:
- Cosmetic Procedures Screening Scale[15]
- Body Dysmorphic Disorder Questionnaire[16]
- Yale–Brown Obsessive Scale modified for BDD[17]
- Dysmorphic concern questionnaire[18]

General questionnaires:
- Derriford Appearance Scale[19]
- Brief Fear of Negative Evaluation Scale[20]
- Hospital Anxiety and Depression Scale[21]

Body image concerns:
- What is the nature of your appearance concern?
- What do you dislike about your appearance?
- Is this a cause of distress or preoccupation?
- When does the feature bother you most?
- Does this impact on your daily functioning?
- Have you had previous treatment to improve your appearance?
- Do you have other body areas of concern?

BOX 81.3 Red flags

Body image concerns that are difficult for others to see
Unrealistic expectations of treatment outcomes
Worrying about body image repeatedly throughout the day or for long periods
Use of camouflaging and cover-up strategies
Constant requests for reassurance
Mirror checking or avoidance of mirrors
Avoidance of social situations
General reduction in quality of life (e.g. no longer socializing)
Disruption in daily activity
Patient presents with numerous photos (of self or of models/celebrities)
Patient presents with detailed ideas of how to improve appearance
Patient has other areas of body image concern
Patient reports multiple previous 'ineffective' consultations or treatments

Further evaluation and treatment

A pre-operative psychological assessment is essential for patients in whom BDD is suspected.[10, 22] If BDD and other psychopathology are ruled out, the patient can then be counselled regarding surgery. If the surgeon still has significant concerns, however, it may be necessary to obtain a second opinion.

Expectations

Determining pre-operative expectations is crucial as poor results are often based on emotional dissatisfaction rather than technical failure.[23] It is therefore important to ask:

- What are your outcome expectations?
- How do you anticipate your life will be different following treatment?
- What if your expectations are not met?

Surgeons must be able to explain to patients how anatomical variations are causing their nasal problem and discuss what surgery can achieve. Through this discussion the surgeon can determine if the patient has realistic expectations.

The use of the rhinoplasty improvement scale is helpful in explaining and counselling patients about realistic post-surgical expectations (**Figure 81.1**). Patients should be informed that moving up one point on the scale is realistic but anything more is unlikely.

ANALYSIS OF THE FACE

In assessing a patient prior to rhinoplasty the analysis should consider the entire face and not simply view the nose in isolation. The analysis begins as soon as the patient enters the consultation room and is formally assessed prior to a detailed assessment of the nose. Attractive faces are deemed to have ideal measurements and angles, which are reportedly based on the dimensions first described by Leonardo da Vinci.[24, 25] This concept has since been extended by Albrecht Duerer,[26] Powell and Humphrey.[27]

Facial symmetry is reported to be the basis for a beautiful face, although minor asymmetry may be associated with the perception of beauty.[28] Many patients are unaware of minor facial asymmetries and, if they discover these in the post-operative period, it could lead to dissatisfaction and misunderstanding. It is therefore important to raise these concerns with the patient and document them pre-operatively.

While a rhinoplasty on an asymmetrical face can lead to dissatisfaction post surgery, correcting an asymmetrical nose which causes the illusion of facial asymmetry can lead to improved facial symmetry without the need for any other surgical procedure.[29, 30]

Symmetry is assessed using midline facial landmarks: a line running through the mid-philtrum of the upper lip, the midpoint of the glabella and the midpoint of the chin indicates a symmetrical face.

Analysis of facial proportions is performed using the 'rule of thirds' and the 'rule of fifths' to assess the face from a frontal view (**Figure 81.2**).[25] Horizontal facial thirds should be approximately equal; the landmarks defining each third are the trichion to glabella, glabella to subnasale and the subnasale to soft-tissue menton. The rule of fifths describes the ideal transverse proportions of the face vertically divided into equal fifths, each fifth approximately equal to the width of one eye; the alar base is equal to the intercanthal distance. The nose ideally occupies one-third of the length of the face and one-fifth of its width. The terms used to describe the constant landmarks of facial anatomy are defined in **Box 81.4**. Other elements to consider are the fullness and position of the lips and protrusion of the chin.

Powell and Humphrey described the ideal angles of the facial aesthetic triangle (**Figure 81.3**).[27] The accepted dimensions of each of the facial angles are:

- nasofrontal angle 115–135°
- nasofacial angle 30–40°
- nasomental angle 120–132°
- mentocervical angle 80–95°.

Facial proportions act as a guide and are helpful in planning procedures but should not be taken as absolute. Each rhinoplasty should respect the individual's wishes, gender and character. It is important to recognize, too, that these ideal measurements vary between ethnicities.[31]

Finally, the analysis of the face should involve inspection of skin type utilizing the Fitzpatrick classification, which divides the skin type based on its colour and its reaction to the first summer exposure (**Table 81.1**).[32] The

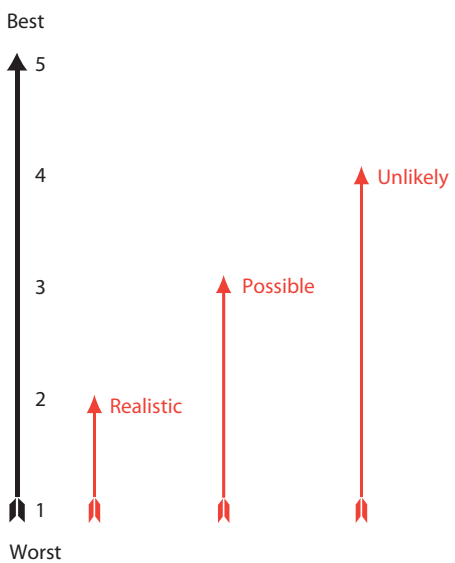

Figure 81.1 Rhinoplasty improvement scale used by the senior author.

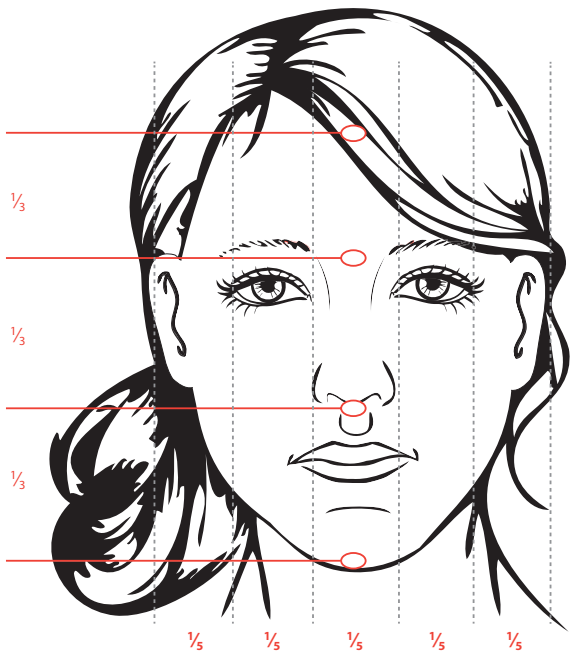

Figure 81.2 The concept of dividing the symmetric face into thirds and fifths.

BOX 81.4 Terminology of facial landmarks

Trichion	Anterior hairline in the midline
Glabella	Most prominent point of forehead in mid-sagittal plane
Nasion	Deepest point of frontonasal angle
Rhinion	Midline point of junction of nasal bones and upper lateral cartilages
Pogonion	Deepest point on outer cortex of mandible
Gnathion	Most inferior point of the chin
Gonion	Most inferior/posterior point of mandible
Menton	Lowest point of mandibular symphysis
Subnasale	Junction of columella and upper lip in mid-sagittal plane

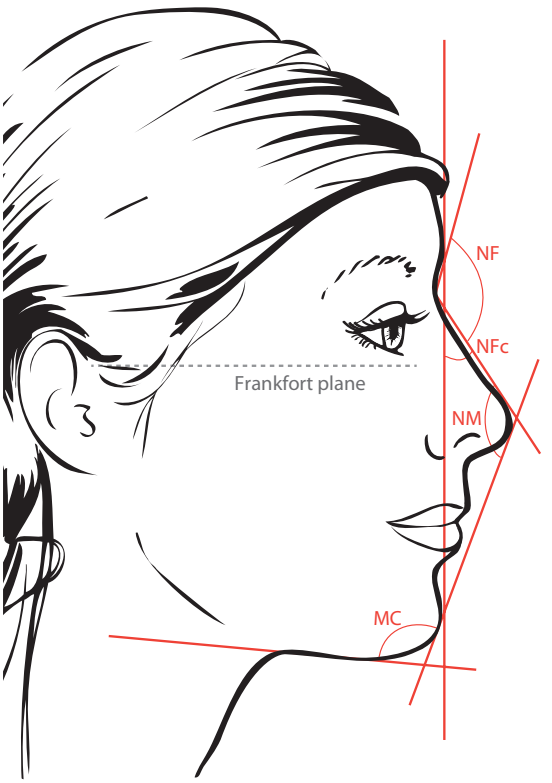

Figure 81.3 Triangles of Powell and Humphrey. Angles of the aesthetic triangle: nasofrontal (NF) = 115–135°; nasofacial (NFc) = 30–40°; nasomental (NM) = 120–132°; mentocervical (MC) = 80–95°.

TABLE 81.1 Fitzpatrick classification of sun-reactive skin types

Skin type	Colour	Reaction to sun
I	Very white or freckled	Always burns
II	White	Usually burns
III	White to olive	Sometimes burns
IV	Brown	Rarely burns
V	Dark brown	Very rarely burns
VI	Black	Never burns

surgeon should also consider the wrinkles on the face both with and without expression. The Glogau classification can be used to characterize progressive degrees of photo damage.[33]

ANALYSIS OF THE NOSE

Analysis of the nose comprises pertains to areas: inspection of the external nose, inspection of the internal nose and palpation.

Inspection of the external nose

Detailed inspection of the external aspects of the nose provides information about the individual nose as well as a comparison to accepted ideal measurements.

- **Skin quality:** This is variable and an assessment of whether the skin is thick and sebaceous or thin is required. Thin skin is unforgiving and minor irregularities are easily detectable; refining and narrowing the nasal tip can be challenging where there is thick skin.
- **Deviations:** The nose is divided into upper, middle and lower thirds. The upper third corresponds to the bony vault, the middle third to the upper lateral cartilages and dorsal septum, and the lower third to the lower lateral cartilages, caudal septum and alar base. Deviated noses are described on the basis of direction of the deviation of each third, e.g. classically described C-shaped, one-sided or S-shaped deviations (**Figure 81.4**). This provides an anatomical assessment of the aetiology of nasal deviation, which is key to surgical planning.
- **Length of the nose:** Nasal length is measured from the nasion to the tip, which is equal to the distance between the stomium and the menton. This can also be calculated mathematically as the distance from the nasal tip to the stomium multiplied by a constant of 1.6. nasal length: NT = TS × 1.6 (**Figure 81.5**).
- **Tip projection:** This is a measure of how far the nasal tip lies anterior to the face. Ideal projection is determined using Goode's ratio, where a line drawn from the alar–facial groove to the nasal tip measures 0.55–0.60 of the distance from the nasion to the nasal tip. A ratio less than this equates to an underprojected nose and greater than this corresponds to overprojection (**Figure 81.6**).
- **Lip–chin relationship:** The horizontal distance from the surface of the upper lip to that of lower lip is normally around 2 mm. The anterior surface of the upper and lower lips rest on the nasomental line in an aesthetic face (**Figure 81.7**).[34] When the chin lies posterior to this line, it is described as retrognathic; when it lies anterior to this line, it is described as prognathic. A retrognathic chin can give the illusion of an overprojected nose and the reverse applies to a prognathic chin. Genioplasty or chin implant procedures are therefore often used in conjunction with rhinoplasty.[35]
- **Dorsum:** The dorsum is inspected from both frontal and lateral views. Tracing the lateral aesthetic lines (also known as the brow–tip line) should reveal

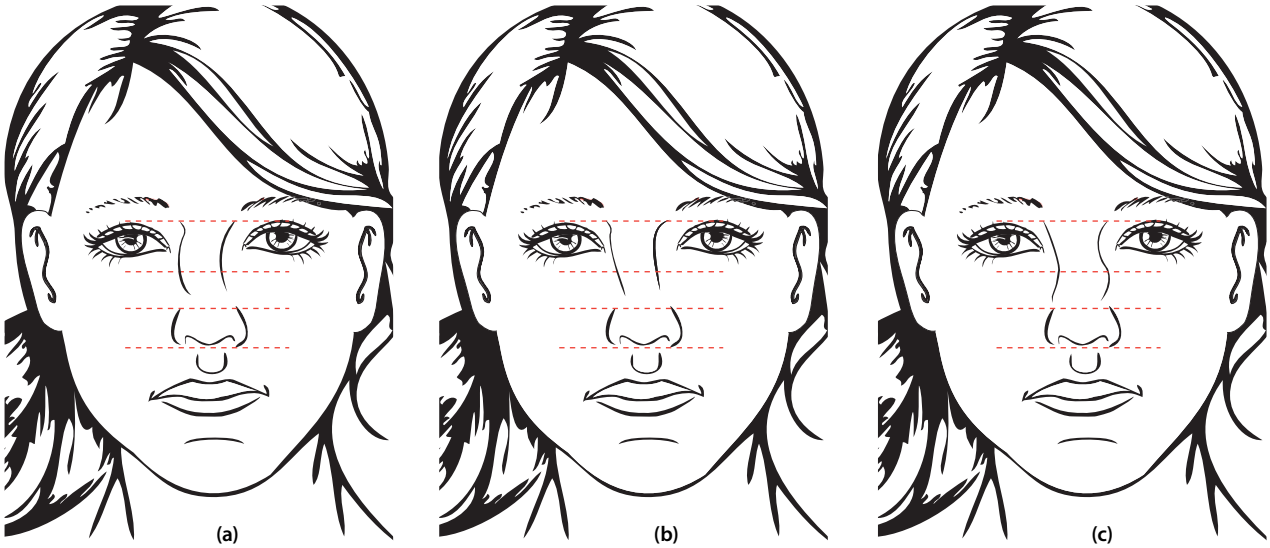

Figure 81.4 Classifying classic nasal deviations using thirds. **(a)** C-shaped, **(b)** one-sided, **(c)** S-shaped.

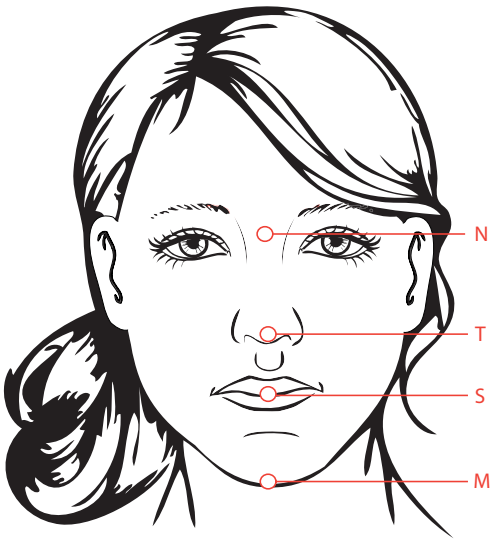

Figure 81.5 Nasal length (NT) = stomium to menton (SM) = 1.6 × TS.

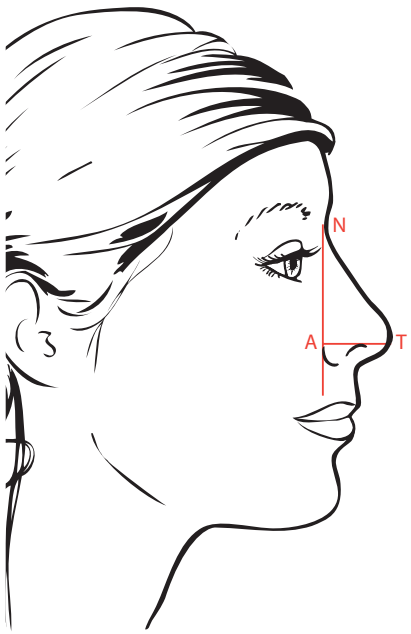

Figure 81.6 Determining tip projection by using Goode's ratio.

a smooth curvilinear line connecting the eyebrow superiorly to the nasal tip inferiorly (**Figure 81.8**). Identification of any irregularities in this smooth curve highlights sources of nasal deformity. In the lateral view, the height of the dorsum is assessed; the dorsum is a straight line in men and in women gently curves with a supratip break delineating the dorsum from the nasal tip. There is wide variation in dorsum height and it often characterizes different ethnicities.

- **Tip configuration:** There are four tip-defining points identified by light reflection (**Figure 81.8**). These represent the domes, the supratip and the infratip. The size and shape of the lower lateral cartilages are assessed, as are asymmetry, bifidity and rotation. Various tip configurations are generally related to these characteristics and to skin thickness. **Figure 81.9** depicts a commonly encountered selection of tip appearances: normal, boxy, bifid, bulbous and amorphous.
- **Tip rotation:** This describes the position of the tip along an arc with its radius centred on the nasolabial angle. The ideal dimension of the nasolabial angle in men is 90–95 degrees and in women is 95–105 degrees (**Figure 81.10**).[36]
- **Columellar show:** The relationship between the ala and the columella is assessed in the lateral view. The amount of visible caudal septum is ideally limited to 3–5 mm (Figure 81.10). This is the distance between two parallel lines drawn from the most anterior and the most posterior parts of the nasal vestibule. A degree of columellar show greater than this may be due to either a hanging columella or abnormalities in the alar margins such notching or retraction.

- **Basal view:** The width of the alar base approximates to the intercanthal distance. The ratio of the width of the dorsum of the nose relative to the alar base should be equal to 80% (see **Figure 81.2**). From the basal view, the nose can also be divided into thirds. The upper third corresponds to the lobule and the lower two-thirds correspond to the columella. A line that transects the columella at the area of medial crural footplate diversion divides the base into two halves (**Figure 81.11**). The overall basal view outline conforms to an isosceles triangle with pear-shaped nostrils lying at an angle of 45° to the vertical.[37] Multiple ethnic variations exist in alar base configuration.

Inspection of the internal nose

Examination of the internal nasal cavity is an essential component of assessment of rhinoplasty in the identification of abnormalities and assessment of donor cartilage sites. Anterior rhinoscopy and nasal endoscopy should be performed.

- **Septum** inspection should be made, looking for deviation, spurs, perforation or the presence of a septal button.
- **Lateral nasal wall and turbinates** inspection can identify congestion, hypertrophy and asymmetry.
- **Internal nasal valve** assessment should be carried out during normal quiet respiration at rest, as exaggerated effortful breathing is likely to precipitate transient internal nasal valve collapse in the normal individual.

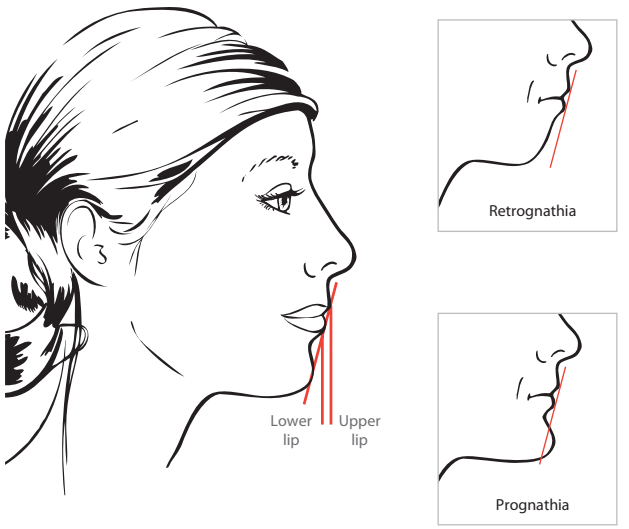

Figure 81.7 Lip–chin relationship.

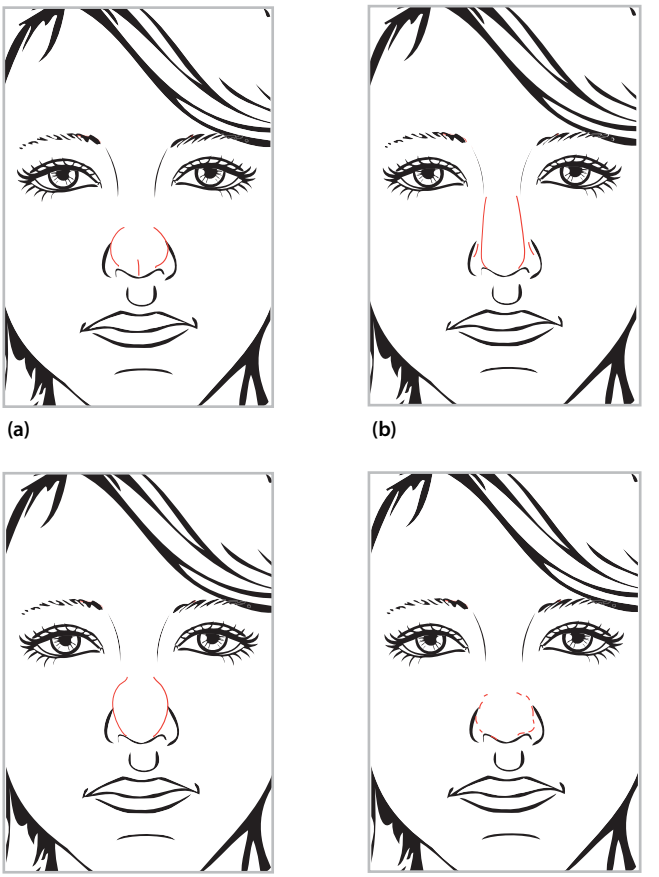

Figure 81.9 Common nasal tip morphology, with 'normal' shown in black outline: (a) bifid, **(b)** boxy, **(c)** bulbous, **(d)** amorphous.

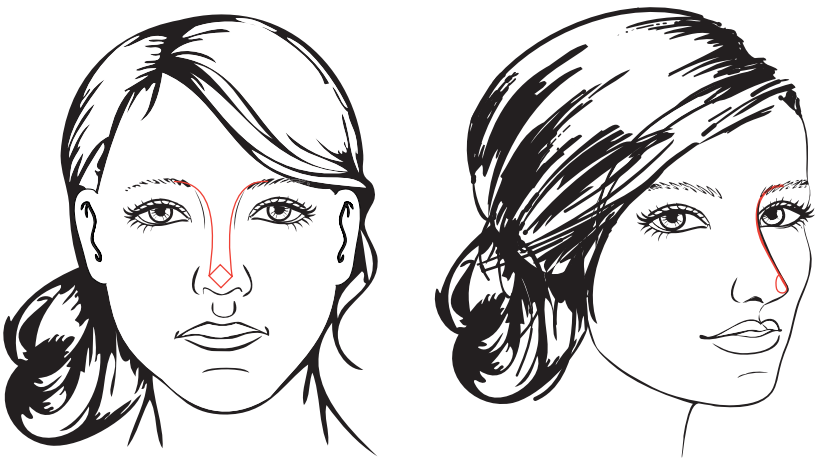

Figure 81.8 Front and right oblique views showing the brow–tip line. Note the four tip-defining points.

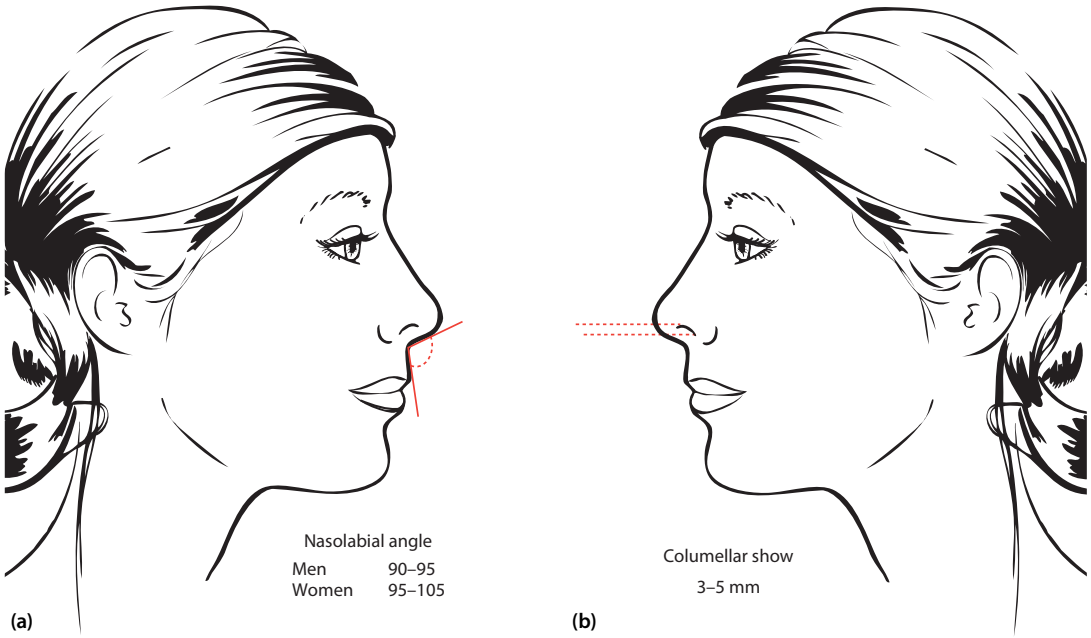

Figure 81.10 (a) Nasolabial angle in men and women. **(b)** Normal columellar show. Labels (a) and (b) angle/show lc a/s.

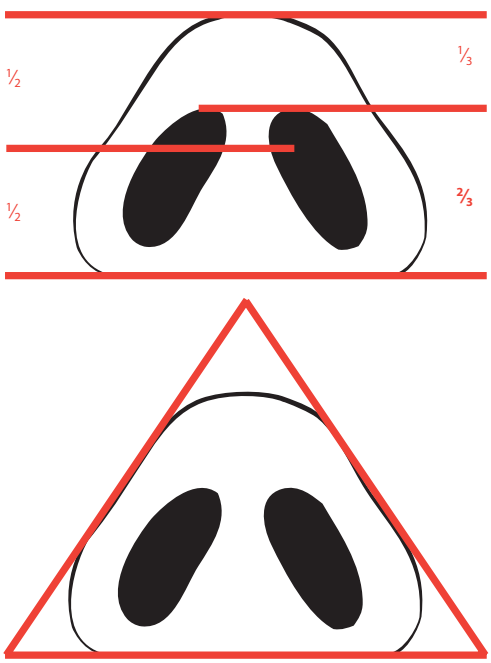

Figure 81.11 Basal view.

- **Cottle's manoeuvre** of opening the internal nasal valve by pulling on the soft tissues of the cheek is non-specific. A better test is to place a Jobson Horne probe in the internal nasal valve to prevent the collapse of the upper lateral cartilage and detect its effect on inspiration.
- **Alar collapse** is a measure of external nasal valve collapse and must be identified pre-operatively. The external nasal valve is not a true valve and is identified by the area bounded by alar cartilages, septum and columella.
- **Endoscopy** can exclude polyps, purulent discharge or residual adenoidal tissue.

Palpation

- **Skin:** Palpate for an assessment of skin texture and elasticity.
- **Irregularities:** Palpate for underlying irregularities that may be due to skin, soft tissue, cartilage, bone or previous graft material.
- **Nasal bones:** Assess the size, position and presence of palpable steps.
- **Tip recoil:** This is an assessment of the strength of the lower third of the nose and provides a palpable measure of the degree of underlying tip support.[38]
- **Alar cartridges:** Palpate for thickness, strength and shape.
- **Spine and septum:** Assess tip support, and confirm the presence and quantity of septal cartilage.

FUNCTIONAL STUDIES

Studies of nasal function are not performed routinely in rhinoplasty assessment and are mainly confined to the research environment. Nasal inspiratory peak flow, acoustic rhinometry and rhinomanometry can be used as objective tests of nasal function and to quantify surgical results. However, the correlation between objective and subjective sensation of nasal patency remains uncertain.[39]

PHOTOGRAPH REVIEW

Standardized photographs are essential for pre-operative planning. They are useful during the discussion with the patient about the proposed surgery and as an intra-operative reference and they are essential for comparison with post-operative results. In order to achieve reproducible photographs a standard patient position is used patient where the Frankfort plane is parallel to the floor; the Frankfort plane is a line that runs from the cephalic tragus to the lower orbital margin (see **Figure 81.3**). The standard photographic views obtained for rhinoplasty are frontal, left and right lateral, left and right oblique and basal. Additional views, which can be of use, are the close-up frontal view, superior view, base–radix view and bird's-eye view.[40–42]

Computer imaging

Computer morphing of the pre-operative photographs has been found to enhance communication with the patient and is associated with higher patient satisfaction.[43] It can also help in judging patient expectations and identifying BDD.[44] However, it is essential to clarify to the patient that image manipulation is only a means of communication and does not imply a specific guaranteed outcome.

CONCLUSION

Following the systematic assessment and examination of the patient, the proposed surgery can be effectively planned with clear surgical steps. It is good practice to commit the surgical steps to a written plan (**Table 81.2**).

TABLE 81.2 Summary of rhinoplasty assessment

Analysis	Assessment	
Patient analysis	What does the patient want? Is it realistic?	
Facial analysis	Symmetry Rule of thirds Rule of fifths	
Nasal analysis	Inspect: external	Skin Deviations Nasal length Tip projection Lip–chin relationship Dorsum–brow-tip line Dorsum–lateral view Nasal tip configuration Tip rotation Columellar show Basal view
	Inspect: internal	Septum Lateral nasal walls Internal nasal valve External nasal valve
	Palpate	Skin Irregularities Nasal bones Tip recoil Alar cartridges Spine Septum
Clinical photographs	Anterior Lateral: left and right Lateral oblique: left and right Basal view	
Computer morphing		
Surgical plan		

BEST CLINICAL PRACTICE

- ✓ First assess the patient, then the face and finally the nose.
- ✓ Develop an operative plan based on the patient's concerns and the results of your analysis.
- ✓ Carefully communicate the operative plan with the patient.

FUTURE RESEARCH

Appropriate patient selection is the ultimate key for successful rhinoplasty. Current research focuses on developing tools that help the surgeon in making that decision. There have been some recent attempts at developing questionnaires to identify those patients who would not benefit from surgery because of unrealistic expectations and to exclude those with suspected body dysmorphic disorder. To date, there has been no consensus and this is the subject of future research.[45–49]

KEY POINTS

- Rhinoplasty is a technically challenging procedure for which both the aesthetics and the function of the nose must be considered.
- Meticulous planning is essential to ensure the best surgical outcomes.
- Successful surgery requires realistic patient expectations, careful consideration of facial aesthetics and a detailed examination of the nose.

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CHAPTER
82

EXTERNAL RHINOPLASTY

Santdeep Paun

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Indications 1144
Anatomy 1144
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SEARCH STRATEGY

Data in this chapter may be updated by a Medline search using the keywords: external, open and rhinoplasty together with review publications and textbooks.

INTRODUCTION

The external or open approach is a firmly established and important technique in rhinoplasty surgery. Its key advantage over endonasal approaches is to afford the ability to assess anatomical deformities by direct inspection of the nasal cartilaginous and bony framework. This in turn allows for easier bimanual sculpturing of the underlying skeletal components and application of sutures and grafts under direct vision. While not an indication for the external approach, there is also a definite advantage for teaching where trainees are able to visualize surgical techniques with ease and these may also be captured satisfactorily with video and photography without the overlying skin and soft-tissue envelope hindering the view.

Limiting surgical tissue dissection to a minimum, as with an endonasal approach, reduces the risk of vascular compromise of the skin–soft-tissue envelope and this approach may therefore be favoured for correction of minimal structural bony dorsal irregularities and minor tip problems. However, the external approach's need for more soft tissue dissection is balanced by the unparalleled view of the nasal structure. In revision surgery, in particular, it facilitates accurate diagnosis in cases where the underlying anatomy is not obvious due to prior surgical resection and scar tissue formation.

The author personally favours this approach for most reconstructive revisions and where the nasal tip needs addressing in primary surgery. Incision refinements and surgical technique have overcome some of the earlier criticisms of a columellar scar and delay in resolution of the supratip skin oedema, and any potential loss of tip projection can be countered by placement of a columellar strut or septal extension graft to maintain support.

The choice of an external approach thus depends not only on the specific pathological anatomical findings but also on the philosophy of the surgeon. However, in deciding to use the external approach, the possible related sequelae should be considered, bearing in mind that the attainment of a predictable satisfying result demands the most atraumatic surgical procedure.

This chapter aims to present some historical aspects and principles of the external approach, outline relevant anatomy and emphasize technical aspects. Advantages with particular reference to grafting of the nasal skeleton and to specific extended indications such as revision rhinoplasty, the deviated nose, nasoseptal perforations, cleft-lip nasal deformities and nasal dermoids are discussed. Pitfalls related to this approach are outlined with the goal of shortening the long and arduous path of the learning process in rhinoplasty.

Mastery of this technique and exploitation of its specific advantages can bring a distinct range of opportunities to the rhinoplasty surgeon.

HISTORICAL ASPECTS

Early references to the elephant trunk incision[1] were made as early as the 1920s and subsequent papers named the approach as the transcolumellar incision,[2] the decortication technique,[3] and finally the external approach,[4] and open or external rhinoplasty.[5, 6] As most texts have adopted the latter three terms, we use them interchangeably in this chapter.

External incisions in rhinoplasty have been used in one form or another in all early descriptions of this procedure. The first such description is believed to have stemmed from India in 600 BC, in which external incisions and an open approach were practised. The first description of an external rhinoplasty via a transcolumellar incision was given by Rethi[2] in 1934 and subsequently by Sercer.[3] In 1974, Goodman advocated the external approach and described a modified transcolumellar incision – the well-known 'butterfly' incision.[4] His original description featured all the key points of incision placement, development of flaps and other surgical techniques. Publications thereafter have mainly served to emphasize the salient points he described. Refinements regarding incision placement, suturing and surgical technique have largely overcome the earlier problems encountered.

HISTORY AND EXAMINATION

The importance of pre-operative assessment in patients seeking rhinoplasty surgery cannot be overemphasized. It is beyond the scope of this chapter to discuss full facial analysis in detail and it is assumed that the rhinoplasty surgeon has a comprehensive knowledge of the relevant concepts.

A complete and discerning history regarding the cosmesis and function, any prior procedures and accurate chronological detailing of post-operative changes is important. Patient anxieties and expectations should be elucidated early in the consultation. The evaluating specialist needs to ensure that such expectations are true and achievable and that the patient's desires are realistic and in keeping with predictable likely post-operative outcomes. Where any doubt exists, sensitive counselling of the patient and referral for psychiatric review is always prudent and surgery is deferred pending this.[4, 5] Pertinent decisions about indications for surgery and potential improvements can then be made.

Diagnosis of the underlying anatomical deformity is essential prior to embarking upon the surgical plan. Inspection and palpation are equally important, particularly when assessing the skin and soft-tissue envelope and minor dorsal irregularities. Within these areas, a further subdivision of underlying skeletal support, soft-tissue thickness and scarring and overlying skin texture will help elucidate anatomical and structural deformities. Intranasal examination may be complemented with endoscopic evaluation to identify the presence of septal deviations, adhesions, nasal valve problems and mucosal disease. Assessment with Cottle's manoeuvre is often advocated but can be non-specific, and lateralizing the upper lateral cartilage with a probe or cotton bud may be a better evaluator.

Approach and technique planning is then discussed with the patient and documented. Standard 2D/3D photography is performed and digital manipulation software can help in discussing potential post-operative changes. This subject is covered in detail in Chapter 81, Pre-operative assessment for rhinoplasty.

INDICATIONS

As has already been indicated, the choice to perform an external rhinoplasty will in many cases be dependent on the training and philosophy of an individual surgeon, recognizing that it is merely an approach to the underlying skeletal structures and not a surgical technique to correct deformity.

However, specific indications for the external approach in rhinoplasty may include:

- congenital deformities such as the cleft lip nose
- extensive revision surgery
- severe nasal trauma
- marked tip deformities including significant rotation and projection issues
- significant septal deviations, especially where high dorsal deviations are present
- situations where assessment of the exact underlying pathology is difficult.

Extended applications of the external approach exploit the excellent exposure of the nasal skeleton and the advantages this affords. It has been advocated for septal perforation repair,[8] access to the nasal dorsum for treatment of nasal dermoids.[9]

ANATOMY

It is important to emphasize salient aspects of the external approach anatomy. **Figure 82.1** shows the anatomical subunits of the nose, which are conveniently divided into thirds. The upper third bony pyramid consists laterally of the nasal bones and the ascending (frontal) processes of the maxilla and the bony septum in the midline. The middle third ('vault') area is formed by the paired upper lateral cartilages inserting just under the caudal end of the nasal bones and their fusion with the midline cartilaginous septum in a T-type configuration. The scroll attachment of the caudal aspect of the upper laterals to the cephalic aspect of lower lateral (alar) cartilages forms the boundary to the lower third of the nose. The upper lateral cartilages thus effectively lie at a slightly lower level to both the nasal bones and lower lateral cartilages. The paired lower laterals form the lower third of the nose, the nasal tip region, and are traditionally divided into

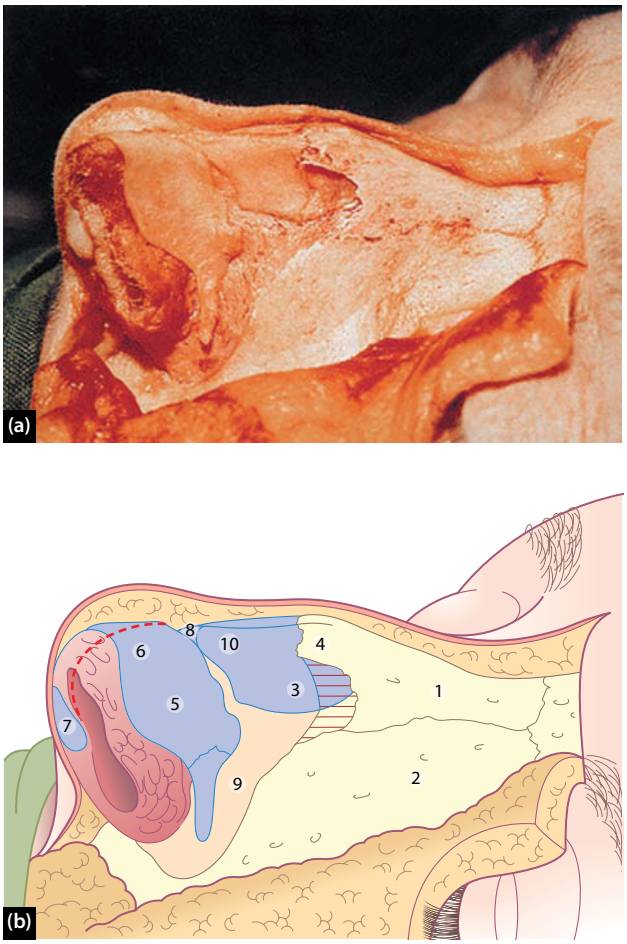


Figure 82.1 **(a)** Lateral view demonstrating the constituents of the anatomical subunits of the nose. **(b)** 1, nasal bone; 2, frontal process of the maxillary bone; 3, upper lateral cartilage; 4, area of overlap of upper lateral cartilage by nasal bone; 5, lateral crus of lower lateral cartilage; 6, dome area within intermediate crus; 7, medial crus of lower lateral cartilage; 8, quadrilateral cartilage; 9, connective tissue; 10, scroll region; 11, shaded area showing removed nasal bone.

the lateral, intermediate and medial crura. It is important to understand that the lateral crura extend laterally but also somewhat cephalically, leaving the most lateral aspect of the nostril's alar margin as being soft tissue alone, devoid of cartilaginous support. The domes and tip-defining points lie within the intermediate crus. The medial crural footplates extend to the lower aspect of the columella and lie just anterior to the caudal aspect of the nasal septum.

The superficial musculoaponeurotic system (SMAS) layer provides a vascular-rich covering to the underlying skeleton, with arterial supply derived from the superior labial and facial artery branches and corresponding venous and lymphatic vessels accompanying these. Exposure of all three parts of the nasal skeleton to some degree with subsequent identification of anatomical anomalies and asymmetries is the key advantage of the external rhinoplasty compared with an endonasal approach.[11]

BASIC PRINCIPLES OF THE EXTERNAL APPROACH

External rhinoplasty lends itself well to a philosophy of conservation of the structural support of the nose by full exposure of the underlyng structures and allowing open access for corrective surgical manoeuvres. It promotes emphasis on augmentation and reorientation of the supportive structures as opposed to reduction and resection.[12] However, certain general points need to be considered. Correct incision placement and meticulous wound closure are essential as the resultant scar should not be an overriding factor in the process of deciding which surgical approach to adopt.

The basic premise is that of a mid-columella incision connecting to bilateral marginal incisions; indeed, it is only this incision that separates it from a delivery-type endonasal approach. Those trained in endonasal rhinoplasty initially often choose to make the marginal incisions first and then join them with the columella incision. It is the author's preference to perform the incision first and then indentify and follow the medial crura outward into the intermediate and subsequently lateral crural areas.

Dissection in the subperichondrial and subperiosteal plane leaves as much soft tissue as possible on the skin flap, thus preserving its viability. In this way the lower and upper lateral cartilages together with the bony dorsum can be exposed to the nasofrontal angle in their undisturbed positions.[13, 14]

Division of the medial intercrural tissue offers access to the caudal septum and premaxillary spine, but it should be left intact if exposure is not indicated, as this intercrural attachment is one of the support mechanisms for the nasal tip. By dividing the upper laterals from the quadrilateral cartilage, the whole of the septum is accessible from the cephalic as well as the caudal aspect, allowing treatment of nasal valve problems, dorsal septal deviations and septal perforation repair.

As intercartilaginous incisions are not used, the valve area is preserved and the important major tip support mechanism of the scroll area is not disrupted. It is, however, important to appreciate that, while the major tip support mechanisms are respected in the external approach, the disruption of the skin soft-tissue envelope from the lower lateral cartilages and the division of the medial intercrural ligamentous fibrous tissue may lead to loss of some of the minor tip support mechanisms, and therefore some tip ptosis should be anticipated in all cases.

SURGICAL TECHNIQUE

Incisions

Fundamental plastic surgery principles dictate that a broken line transcolumellar incision will leave a less visible scar, rather than a single line horizontal incision which will be both more noticeable and prone to contraction. Commonly used incision variations include the step, gullwing and inverted V-type configurations. The author prefers the latter approach as this gives a near inconspicuous scar when properly closed.[16] If the columella is deemed too short in relation to the intended tip projection, as may occur, for example, in

cleft-lip rhinoplasty, a V incision made at the base of the columella to perform a V–Y lengthening procedure may be indicated.[17] An alternative forked flap has also been described.[18]

The columella incision should be situated in the upper two-thirds, normally at its narrowest point, to ensure the medial crural footplates provide adequate support, thus preventing a depressed scar (**Figure 82.2a**). In the lower third of the columella, the medial crura bend backward towards their attachment to the caudal septal area and thus the skin of the columella in this area is unsupported. It is essential to protect the integrity of the caudal end of the medial crura just beneath the incision to prevent post-operative notching in this area. This may be done by initially making only a very superficial columellar incision, cutting just through the skin; the vertical columellar parts of the marginal incisions are then placed 1.5–2 mm inside the vestibule and joined by careful undermining of the columellar skin with sharp dissecting scissors. These blades of the scissors can then be used as a guard upon which the columella incision is completed.

The midline aspects of the medial crura are now identified with sharp dissection and this is used to extend the incision upward towards the intermediate crural region. Ensuring adequate exposure of the cartilage, ideally in a subperichondrial plane, the marginal incision is then continued more laterally using angled Converse/Walter scissors with a spreading movement hugging the caudal aspect of the cartilage, followed by cutting of the overlying soft tissue (**Figure 82.2b** and **c**). To obtain adequate exposure of the nasal skeleton, the marginal incision should be extended at least halfway along the lateral crus but can be extended further laterally if dissection of the lateral most aspect of the lateral crus will be required.

Dissection of the soft-tissue envelope

Dissection of the soft-tissue envelope in the subperichondrial and subperisoteal plane is desirable to ensure minimal bleeding. Dissection after exposure of the medial crura should be continued in a lateral direction up to the hinge area, hugging the lower lateral cartilage, with further extension in a cephalic direction to the scroll area (**Figure 82.2d**). To free the cartilaginous vault, it is easy to make a false passage into the SMAS. To prevent this, dissection should be commenced in the midline between or just cephalic to the domes. It can be helpful to incise the perichondrium at the caudal end of the cartilaginous vault vertically in the midline, after which subperichondrial dissection can proceed from medial to lateral and in a cephalic direction. This can leave a useful subperichondrial flap that can be resutured in the midline, if required, to help with camouflage of underlying irregularities, particularly in thin skin noses.

Conversely, a thick supratip soft-tissue envelope can be thinned at a later stage if required, although this is done very conservatively to prevent compromise of the vascular supply to the overlying skin. A potential complication of the external approach is prolonged supratip oedema and occasionally a soft-tissue pollybeak as a result of dissection in the wrong plane disturbing the integrity of the transverse nasal muscle.

Dissection of the soft tissue of the bony pyramid in a subperiosteal plane starts with an incision made 2–3 mm parallel to and above the caudal end of both nasal bones. It is of great importance to palpate the edge of the nasal bone before making the incision, to prevent separation of the upper laterals from the bony pyramid, a pitfall that can only be corrected with a camouflaging onlay graft. The sharp side edges of a Joseph periosteal elevator are engaged along the incision to facilitate the raising of a subperiosteal flap over the bone.

The aim of the open approach is to identify and adequately expose underlying anatomical deformities and facilitate correction, and raising of the skin and soft-tissue envelope need only to extend to the areas of concern. More extensive dissection laterally over the doral bony skeleton has been advocated recently (an extended open approach) to facilitate powered instrumentation to create precise lateral osteotomies.

A potential disadvantage of the external approach is the difficulty assessing the supratip area and the desired tip projection, due to the lack of traction of the soft tissue prior to closure of the columella incision. Final assessment of these areas should thus be made after preliminary closure of the incision. Adjustment is still possible either by cartilage vault reduction and, if insufficient tip projection, by adding an onlay tip graft through the marginal incision or a shield graft, which can be sutured into place after reopening the transcolumellar incision.

In case of grafting procedures for augmentation, care should be taken that the overlying soft tissue has sufficient viability. Blanching of the skin over an augmentation graft is a warning sign which should not be neglected. A slight reduction of the graft size will prevent possible skin necrosis.

Access to the nasal septum

The nasal septum can be accessed by division of the soft tissue between the medial crura of the lower lateral cartilages, effectively dividing the membranous septal area (see **Figure 82.2f**). This will, however, disrupt one of the minor tip support mechanisms so may be best avoided if no cartilaginous material is available to provide structural support to maintain post-operative tip projection. An alternative exposure can be gained by a traditional separate hemitransfixion or Killian's incision.

Provision of a stable cartilaginous base is critical in all nasal tip surgery. If a columellar strut or septal extension graft is required, it is placed in a well-defined pocket between the crura, and extends from 2 mm above the anterior nasal spine to the angle between the medial and intermediate crura. The sandwich construction is fixed by mattress sutures which must not be placed above this angle in order to prevent loss of the columella–lobular ('double break') angle.[19, 20] To prevent asymmetry at the caudal plane of the columella and in dome height, it is important to fix the medial crura in the right parallel position temporarily with a needle after which final fixation with mattress sutures is accomplished (**Figures 82.2g** and **82.3**). The cartilaginous strut may also be used to correct buckled medial crura, strengthen weak medial crura, correct tip asymmetries and provide a stable base for the application of tip grafts.

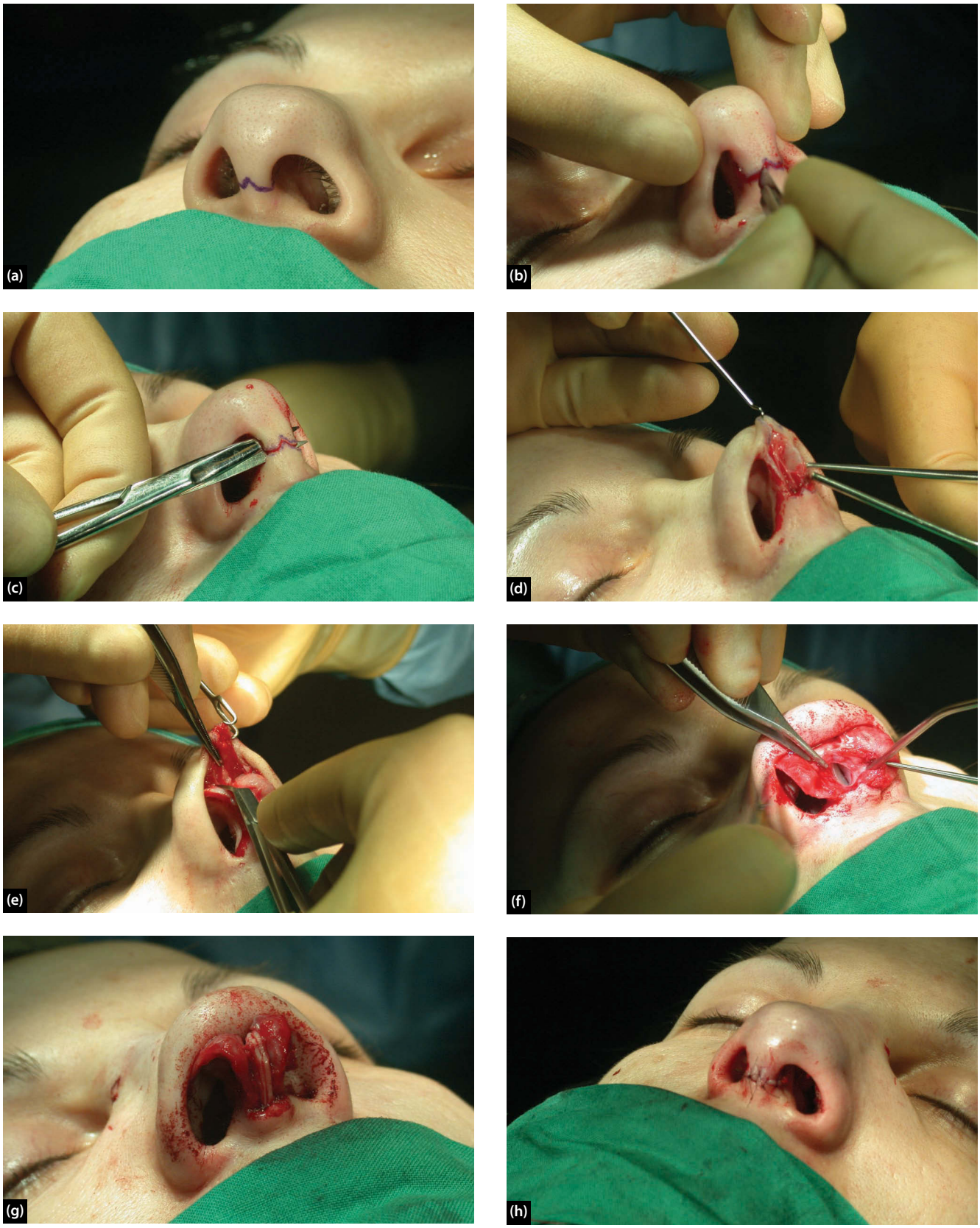


Figure 82.2 External rhinoplasty approach to correct an underprojected, asymmetric bulbous tip. **(a)** Mid-columella inverted 'V' incision. **(b)** Superficial incision made through the columella skin. **(c)** Iris scissors placed behind the incision to protect medial crurae. **(d)** Exposure of the medial crurae with development of the columella skin flap. **(e)** Dissection over the nasal domes with converse scissors. **(f)** Exposure of the caudal septal cartilage by dissection between medial crurae. **(g)** Columella strut placed between medial crurae. **(h)** Closure of incision after correction of boxy tip deformity.

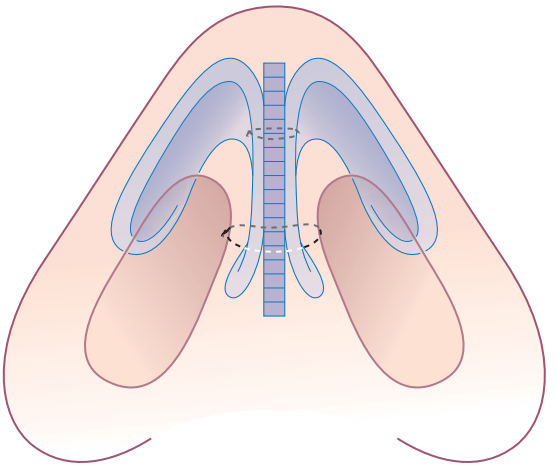


Figure 82.3 Columella strut of autogenous septal cartilage for extra tip support fixed by mattress sutures to the medial crura.

Closure of the transcolumellar incision

Meticulous closure is imperative with slight eversion of the wound edges (**Figure 82.2h**). Authors have favoured both fine non-absorbable suture material (6/0 ethilon or prolene) although the use of a rapidly absorbable suture such as 6/0 Vicryl Rapide negates the need for suture removal, which can prove very uncomfortable. To prevent tension, it can be helpful to place an initial subcutaneous absorbable suture, although this is not usually necessary. Between five and nine fine sutures are then used to close the incision with attention importantly focused to the lateral edges of the columella where irregularities may be most visible. The vertical incisions along the vestibular edge are closed and a single suture to approximate the lateral marginal incision normally suffices.

After closure of the incision, a smooth skin line of the columella from a basal and lateral view should be ensured. The skin sutures are removed, if required, 5–7 days postoperatively. While not favoured by the author, the use of tissue glue has also been shown to be an effective alternative method of closure.[21]

SPECIFIC APPLICATIONS

The bony pyramid in external rhinoplasty

Exposure of the upper third of the nose allows more accurate diagnosis and precise correction of dorsal abnormalities, thus avoiding irregularities that can arise from a closed procedure. The subperiosteal dissection should not extend more than halfway along the nasal bones.[22] The exception to this is when an extended dissection along the most lateral aspect of the bony vault to allow for powered lateral osteotomies such as with a Piezo device are planned.

A direct systematic examination is possible of the individual components of the bony vault. The size, shape and position of both nasal bones and bony septum, as well as the thickness of the overlying skin-soft tissue envelope in the region of the rhinion and nasion, are assessed individually and in relation to their effect on the nasofrontal angle and the width, height, dorsal profile and contour of the upper third.

The open approach allows the use of a burr or Piezoelectric device to deepen the nasofrontal angle. Conversely, the angle can be deepened or set in a more cephalic position by precise application of soft-tissue onlay radix grafts of temporalis fascia or slivers of autogenous cartilage. Such implants can also be secured in an accurate position via this approach.

The principles and techniques of bony dehumping together with lateral, medial oblique and intermediate osteotomies are the same for both the endonasal and open approaches although the latter has the added advantage of allowing direct vision, particularly when powered instruments are used. It can be easier, however, to remove medial bony wedges in a trapezoid bony vault with an open approach.

The middle nasal vault

The 'nasal valve area' is the smallest cross-sectional area in the nasal airway. Its boundary is formed by the caudal end of the upper lateral cartilage, the head of the inferior turbinate, the floor of the nose, the nasal septum and the intervening tissue surrounding the pyriform aperture. Rhinoplasty can compromise the nasal valve, particularly in patients with short nasal bones, a high bony–cartilaginous hump and weak upper lateral cartilages.[23] Frequently, there is an additional corresponding aesthetic defect of a 'sunken' or 'pinched-in' middle third. Such an inverted V-type deformity is a consequence of either excessive resection of or collapse of the upper lateral cartilages inferomedially due to inadequate support after removal of a dorsal hump. The nose displays a 'washed-out' appearance with prominence of the caudal edge of the nasal bones. There may be associated internal nasal valve collapse giving rise to nasal obstruction.

Placement of 'spreader grafts' to open up the nasal valve area and angle was initially described via an endonasal approach thereby improving both function and cosmesis (**Figure 82.4**).[24] The external approach allows easier and more precise placement and suture fixation of such spreader grafts, minimizing risk of displacement. These cartilaginous strips are placed longitudinally between the upper lateral cartilage and septum. The mucosa between these cartilages is often divided but, based on Sheen's original work,[32] this should be avoided and rather the spreader graft placed extramucosally. The functional improvement has been difficult to quantify objectively but subjective improvement is to be anticipated. Placement via an external approach allows for accurate visualization but, when required, can be equally well placed endonasally[33] into tight submucoperichondrial pockets and held with tissue glue or with percutaneous trans-septal sutures if needed. Unilateral placement of spreader grafts may also correct asymmetries of the dorsum.

'Autospreaders'/spreader flaps can be an effective and simple alternative and negates the need for a separate cartilaginous source (**Figure 82.5**). When lowering the

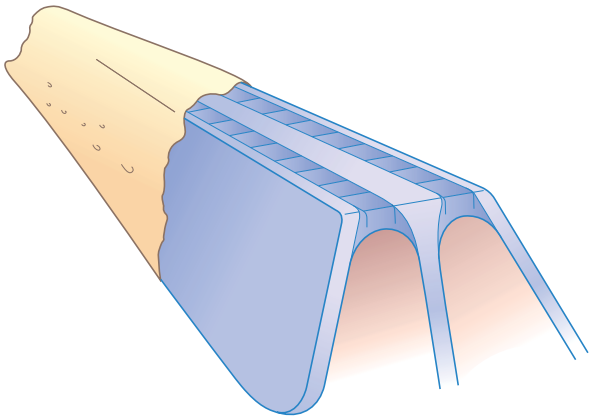


Figure 82.4 Shaded areas showing placement of spreader grafts.

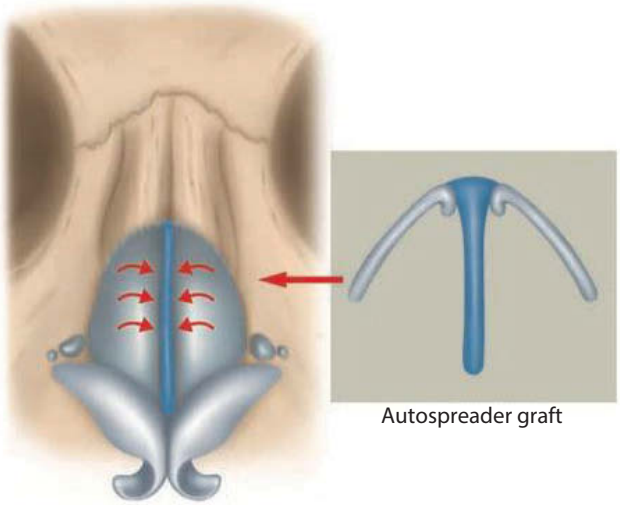


Figure 82.5 Autospreader graft/spreader flap created by turn in of upper lateral cartilages.

cartilaginous dorsum, the upper lateral cartilages are separated extramucosally from the septal cartilage and the superior-most aspect of its cephalic edge dissected off the underside of the bony vault. The midline septal cartilage is then lowered but the upper laterals are left intact and infolded to create such spreader flaps, mimicking the effect of spreader grafts. These can be an effective way of avoiding mid-vault narrowing but alone are unlikely to proffer any functional benefit.

The open approach exposure also facilitates extended roles of spreader grafts to include their use as part of lengthening an overly rotated nose with articulation onto septal extension grafts, maintenance or reconstruction of the dorsal nasal roof, straightening of a high dorsally deviated septum and recreation of the dorsal aesthetic lines.[25]

Nasal tip surgery

Nasal tip surgery has perhaps been the major beneficiary of the open approach since it exposes the structural components of the tip in their natural undisturbed position. It allows unparalleled diagnosis of the various deformities and asymmetries as well as facilitating precise surgical manipulation of the tip cartilages and suture fixation of grafts. In particular, it allows the visualization and correction of minor asymmetries, thus adding extra surgical finesse.

While it is beyond the scope of this chapter to discuss nasal tip techniques in detail, some highlights of tip surgery that benefit most by the open approach are featured. Altering tip projection and rotation by modelling the alar cartilages is based upon the 'tripod' theory.[5] This theory states that the structural framework of the nasal tip is based on the two lateral crura and the conjoined medial crura, each forming one leg of the tripod (**Figure 82.6**). This allows an understanding of the effect on the tip position by altering the size and position of the medial or lateral crura. For instance, if the medial and lateral crura are reduced in length, the tip is deprojected; if they are augmented, projection is achieved. Superior rotation is achieved by shortening the lateral crura or, alternatively, by lengthening the medial crura causing rotation at the 'hinge' region.

Problems encountered may be conveniently thought of as being due to under- or over-rotation, under- or over-projection, width problems or intrinsic tip deformities. Manipulation of any part of the tripod model normally leads to predictable changes in both the projection and rotation of the nasal tip and some examples are described below. All aspects of tip surgery can be performed in a more controlled fashion and with a high degree of symmetry by using the external approach.[7, 27, 28]

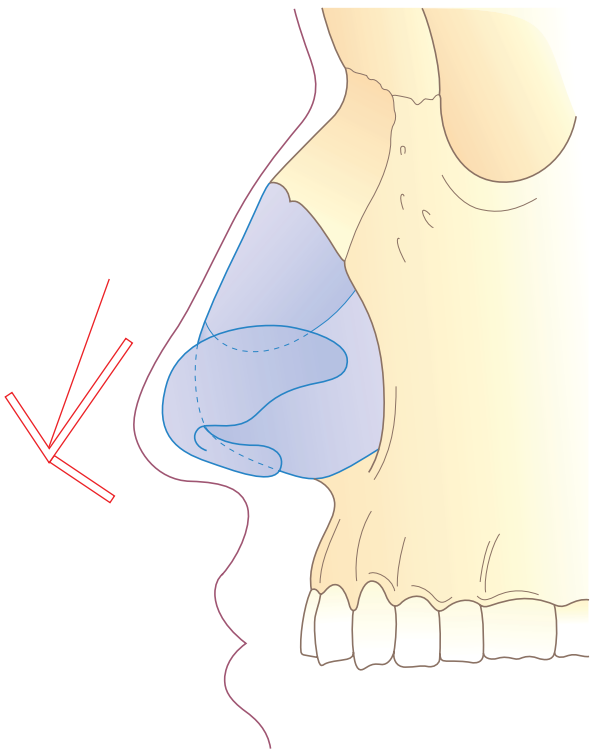


Figure 82.6 Tripod complex of the lower third of the nose. The conjoint medial crura comprise one leg of the tripod, while the lateral crura comprise the other two legs.

ROTATION DEFORMITIES

Correction of the under-rotated tip can be effected with various manoeuvres, based on the tripod theory. Rotation changes are usually linked with some associated projection change.

Lateral crural steal techniques with recruitment of the lateral crura medially using domal suturing creates tip projection and rotation. Conversely, resection and overlay of the lateral crura (lateral crural flap/overlay technique **Figure 82.7**) produce rotation with deprojection. Such a technique is generally used to shorten the nose as well when overprojection is problematic. Plumping grafts and columellar struts are also used to create an illusion of rotation.

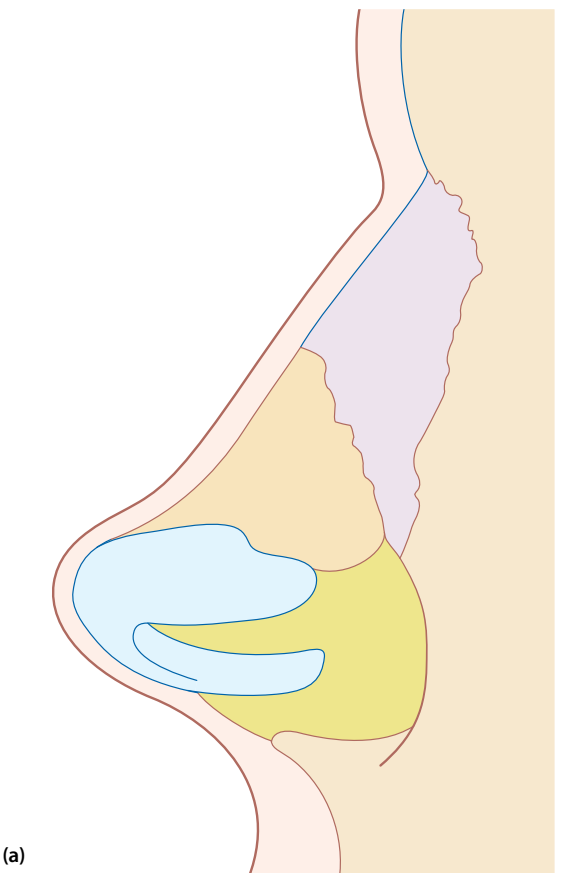
An overly rotated nasal tip is often challenging to correct, particularly when it is a result of prior surgery. It occurs most often due to a combination of factors at the original surgery such as resection of the anterior septal angle, or the visoring effect of excessive cephalic strip excision of the lower lateral cartilages perhaps together with other rotation manoeuvres involving the lateral crura. Options for correction are more limited with this situation and soft-tissue changes limit how much counter-rotation occurs. The mainstay of management is placement of a caudal septal extension graft to effectively lengthen the nose (**Figure 82.8**). Extended spreader grafts are then used to try to stabilize the septal complex and the lower lateral cartilages are then rotated downwards and fixed to the extension graft.

Again using the tripod theory, division and overlap of the medial crura will create counter-rotation although this does also deproject the tip. Finally, a graft in the tip/infratip area will give an illusion of counter-rotation and increased length of the nose and is best employed in addition to, rather than instead of, the other listed procedures when required. This is best avoided, however, in thin-skinned individuals where grafts in the tip region are potentially easily visible.

PROJECTION DEFORMITIES

Projection of the nasal tip is often desirable in rhinoplasty surgery. Both external and endonasal rhinoplasty approaches can create post-operative ptosis, so attempts to maintain adequate projection are important. Dome suturing, so often used to define the nasal tip by increasing triangularity and narrowing, may also act to project the tip somewhat. Used alone, a small amount of increased projection and rotation can be achieved. When further projection is required, the lateral crural steal is a workhorse technique that can also rotate the tip. It is important not to overtighten sutures as this can create a pinching effect.

The 'tongue-in-groove' technique of septocolumellar suturing is a further option and usefully allows setting of projection and rotation of the nasal tip (**Figure 82.9**). A disadvantage of this method is the rigidity and lack of mobility such a procedure imparts to the tip but it is



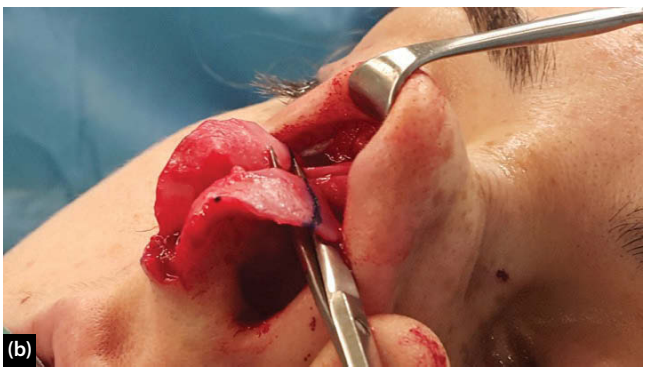


Figure 82.7 **(a)** and **(b)** Lateral crural flap/overlay – the lower lateral cartilage is divided laterally and overlapped to deproject the tip. This also creates a degree of rotation.

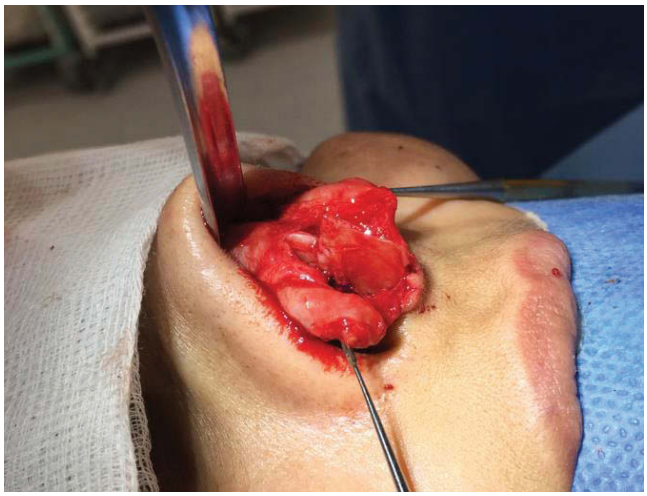


Figure 82.8 Septal extension graft placed in an 'end-to-end' fashion.

generally well tolerated in most patients. This technique can cause a degree of columellar retraction and over-rotation of the tip if the distance between the medial crura and caudal septum is excessive. A septal extension graft can be used to counter this, adding additional security of strength and base stability to the nasal tip complex. Columellar struts may help strengthen inherently weak medial crura, thereby creating projection, but they are generally best used in addition to other techniques as, alone, they may not be able to counter contraction post-operatively. Using a permanent suture between the upper lateral cartilages and columellar complex provides stability in this regard.

Grafts may also have a part to play. Shield and tip grafts work well in thicker-skinned patients and can create a final finesse to a poorly projected tip.

Deprojection of the 'tension' nose is a less frequently encountered problem in revision surgery. A full transfixion incision will divide the medial crural footplate attachment as they curve backwards to the caudal septum, thereby disrupting a major tip support mechanism, predictably creating some post-operative tip deprojection that is an easy initial step in correcting this deformity. This may need to be combined with division and overlay of the medial, lateral or both crura, depending on the rotation requirements. The 'lateral crural flap' alone creates deprojection and rotation and, in a similar way, the medial crural flap technique will deproject and counter-rotate the nose (see **Figure 82.7**). If the rotation needs no altering, an equal amount of overlapping in both areas can be performed, thus counterbalancing any rotation changes.

Excision of the anterior nasal spine has also been described[35] but risks bleeding and the potential for some columellar retraction.

INTRINSIC TIP DEFORMITIES

Pinched nasal tip deformity

By far the most common cause of a pinched nasal tip deformity is iatrogenic weakening of the lower lateral

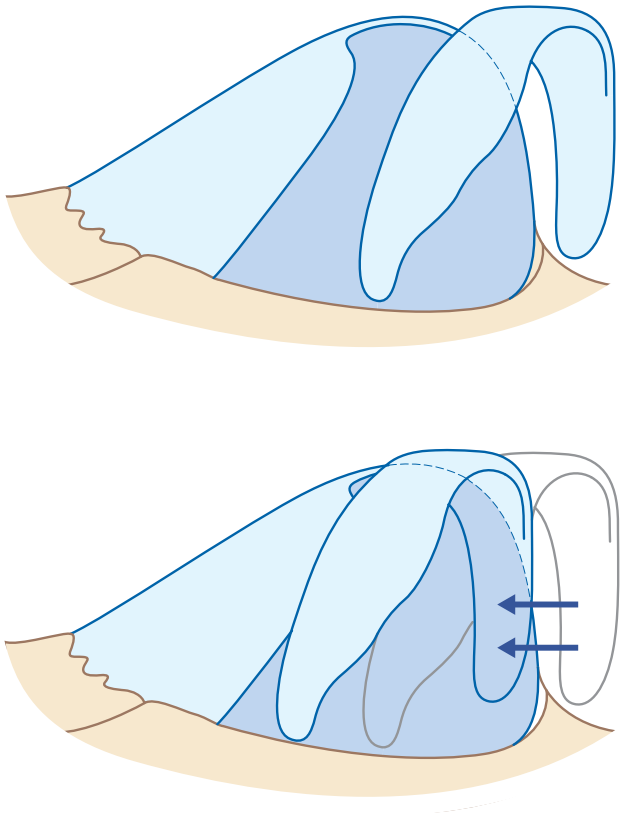


Figure 82.9 Tongue in groove technique of septocolumellar suturing.

cartilages due to over-resection of the cephalic edge of the lower lateral cartilages with subsequent weakening of the intact rim strip. The useful edict of leaving behind more cartilage than that resected should always be remembered; the author recommends an absolute minimum of 6 mm cartilaginous support but leaving more may be more favourable. The author now rarely resects the lateral crus cephalic cartilage but instead attempts to reorientate in such a way that the caudal edge lies at a higher level to the cephalic border. Aggressive domal suturing with its resultant alteration in tip orientation and dynamics can also cause notching in the dome region, predisposing to a pinched tip effect.

The lateral crura should have an outward convexity of the posterior alar rims and gentle rounding in the dome region; specifically, there should be no pinching of the lateral alar walls. While for minor deformities, an endonasal approach may prove adequate for placement of supporting grafts in primary surgery or to correct prior overzealous tip suturing, the open approach allows for accurate anatomical analysis of the underlying deformity of the lower lateral cartilages which can then be repositioned and modified as required. Small specific pockets allow batten grafts to be inserted to correct concavities caused by weakness of the cartilage. An isolated aesthetic deformity caused by inherent concavity of the lateral crus may be corrected by complete mobilization of the lower lateral cartilage from the vestibular skin. An incision is then made just lateral to the domal area and the lateral

crus flipped over such that the concavity now becomes a convexity. The rotated crus is then sutured to the medial segment (**Figure 82.10**).

The external approach remains the author's favoured method for accurate evaluation of the orientation, integrity and strength of the alar cartilages. Augmentation using septal or auricular cartilage to fashion alar battens or lateral crural strut grafts provides stability and strength to the weakened alar cartilages, thus correcting both aesthetic and functional aspects of the deformity. Alar rim grafts can further recreate convexity and rounding of the nasal tip contour as assessed on the frontal and basal views.

Bossae formation

Knuckling of the lower lateral cartilages in the domal area forms so-called 'bossae'. The inexperienced rhinoplasty surgeon may not be aware of the triad of thin skin, strong alar cartilages and bifidity of the tip which together predispose to their formation when there is an excess cephalic strip reduction and inadequate narrowing of the domes.[38] Post-operative scar contracture in this area causes the deformity.

Treatment options include trimming or resection of the knuckled areas with suture reconstruction of the lower lateral cartilages. Covering the area with a camouflage graft may also help correct any minor residual deformity.

Alar retraction

Overzealous cephalic strip resection can lead to alar retraction due to the visoring effect caused by contraction as healing occurs.[39, 41] An absolute minimum of 6 mm residual cartilage is recommended but, in the presence of an anatomically narrow alar cartilage, this may need to be revised. If vestibular mucosa is not preserved, this too can contribute to contracture and promote further retraction. Correction with cartilage grafting placed into a snug pocket fashioned through a marginal incision may improve minor defects. For a more severe deformity, a composite cartilage graft, usually fashioned from the concha of the opposite ear, is taken.[42] This is placed into a space created by dissection of the alar rim away from the residual lower lateral cartilage, allowing the alar rim to be displaced caudally. An alternative is to dissect space between the upper and lower lateral cartilages and place a firm (ideally septal or rib) spacer graft into this area, pushing the lower lateral crus caudally.

Hanging collumella and retraction

The hanging columella can be a very unaesthetic deformity. Options include resection of the caudal and/or membranous septum, which is the main cause. However, in the presence of prominent medial crura, resection of the caudal aspect of the crura or occasionally vertical division may resolve the deformity.[43] The 'tongue-in-groove' method of suturing the medial crura to the septum described previously can be an effective alternative.[36]

Columellar retraction is often a consequence of overresection of the caudal septum at primary surgery. The lack of support in this area causes gradual contraction with time. Placement of a columellar strut sutured between the medial crura is a treatment option, as are plumping grafts placed in the premaxillary area. More substantial retraction can be improved with cartilaginous septal extension grafts. These can be tailored to project either the whole retraction or variably the upper or lower part forwards, dependent on the need for rotation of the tip.

Revision rhinoplasty

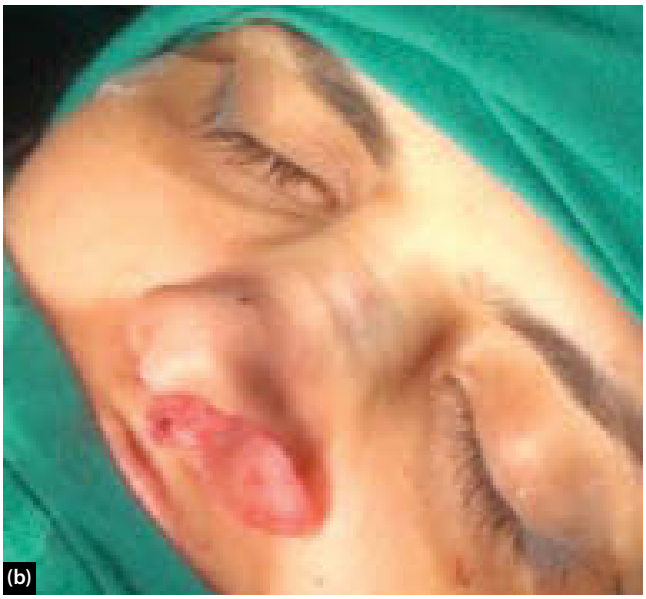
Revision rhinoplasty is undoubtedly one of the most challenging operations undertaken by the facial plastic surgeon. The dawn of a social media generation has led to increased public awareness of all aspects of cosmetic surgery, including the need and desire for revision procedures, with the newly informed patient becoming more critical of post-operative results. An unprecedented number of media articles on aesthetic surgery appear to be increasing patient expectations. As contemporary techniques evolve, the modern rhinoplasty surgeon is constantly seeking an ultimate post-operative result that will please both the discriminative patient and surgeon alike.

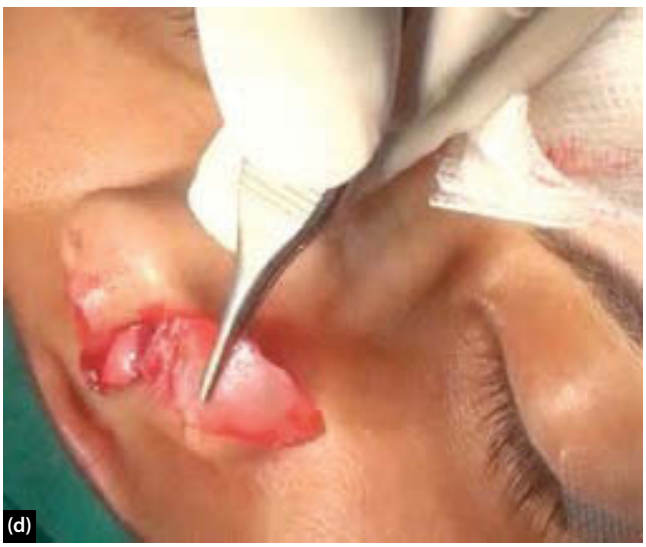
Various authors have reported an increase in the number of revision cases, which may be a reflection of the greater popularity of rhinoplasty and the enhanced expectations and discrimination of both the surgeon and patient.[30, 31]

The key to successful revision procedures is the ability to correctly diagnose underlying deformity in the first instance with a view to formulating a surgical plan. Very often, this can be challenging given soft-tissue contracture following prior surgery. The open approach, of course, allows accurate visualization of the deformity and simplifies accurate correction, which may require advanced techniques, including augmentation procedures. Structural grafting and relocation of tissue with the aim of producing predictable favourable long-term results is facilitated. Scar tissue may also be more easily identified and excised.

The deviated nose

The external approach to the deviated nose lends itself well to accurate correction of such a deformity due to the added exposure it provides and the ability to place corrective grafts. When excising a bony hump in the presence of a bony pyramid deviation and unequal height of the nasal bones, the plane of the osteotome may be altered to allow this. Alternatively, the use of powered instruments such a Piezo device under direct vision will allow accurate reduction of the dorsal bone and cartilage alike. Osteotomies can also be performed sequentially under direct vision. For example, if the nose deviates to the right, the first step is to mobilize the left nasal bone and reposition it in its normal position; the next step is to position the bony septum in the midline; and, finally, the right nasal bone is repositioned in its normal position.[22] Again, with extended lateral dissection, a Piezo saw can be used under direct vision to create the lateral osteotomies.





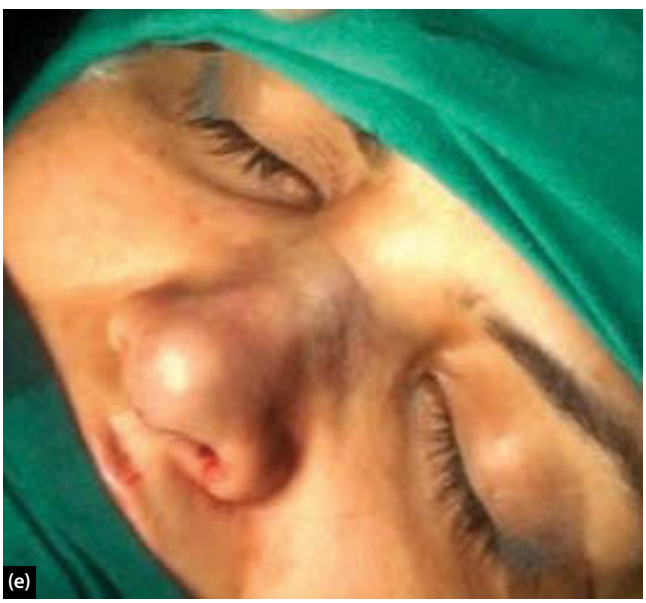


Figure 82.10 (a) Unilateral concavity of lateral crus. **(b)** Dissection of lateral crus from underlying vestibular skin. **(c)** Concave lateral crus divided just lateral to dome. **(d)** Concave segment flipped over to create convexity. **(e)** Convexity now seen in final result.

A deviation of the lower two-thirds of the nose is usually due to a C-shaped dorsal deviation of the nasal septum, possibly complicated by previous surgery, which may have disrupted the union of the upper laterals to the septum. In mild cases, the dorsal aspect of the septum is shaved on the convex side and sutured to the upper lateral cartilage. If this is not sufficient to correct the deviation, a unilateral spreader graft is placed between the dorsal septum and the upper lateral cartilage.[20] The spreader graft acts as a stent as well as opening the nasal valve area. Any residual deformity is corrected by an onlay graft (**Figure 82.11**).

Dorsal augmentation

For grafting purposes, autologous septal or auricular cartilage remains the ideal standard and this appears to be supported by most authors. Options may be limited by prior surgery and the option of the autogenous or homologous irradiated costal cartilage must be considered. Alloplastic materials are reserved for cases where there is minimal residual cartilage available and the risks associated with infection and possible extrusion should be discussed with the patient pre-operatively.

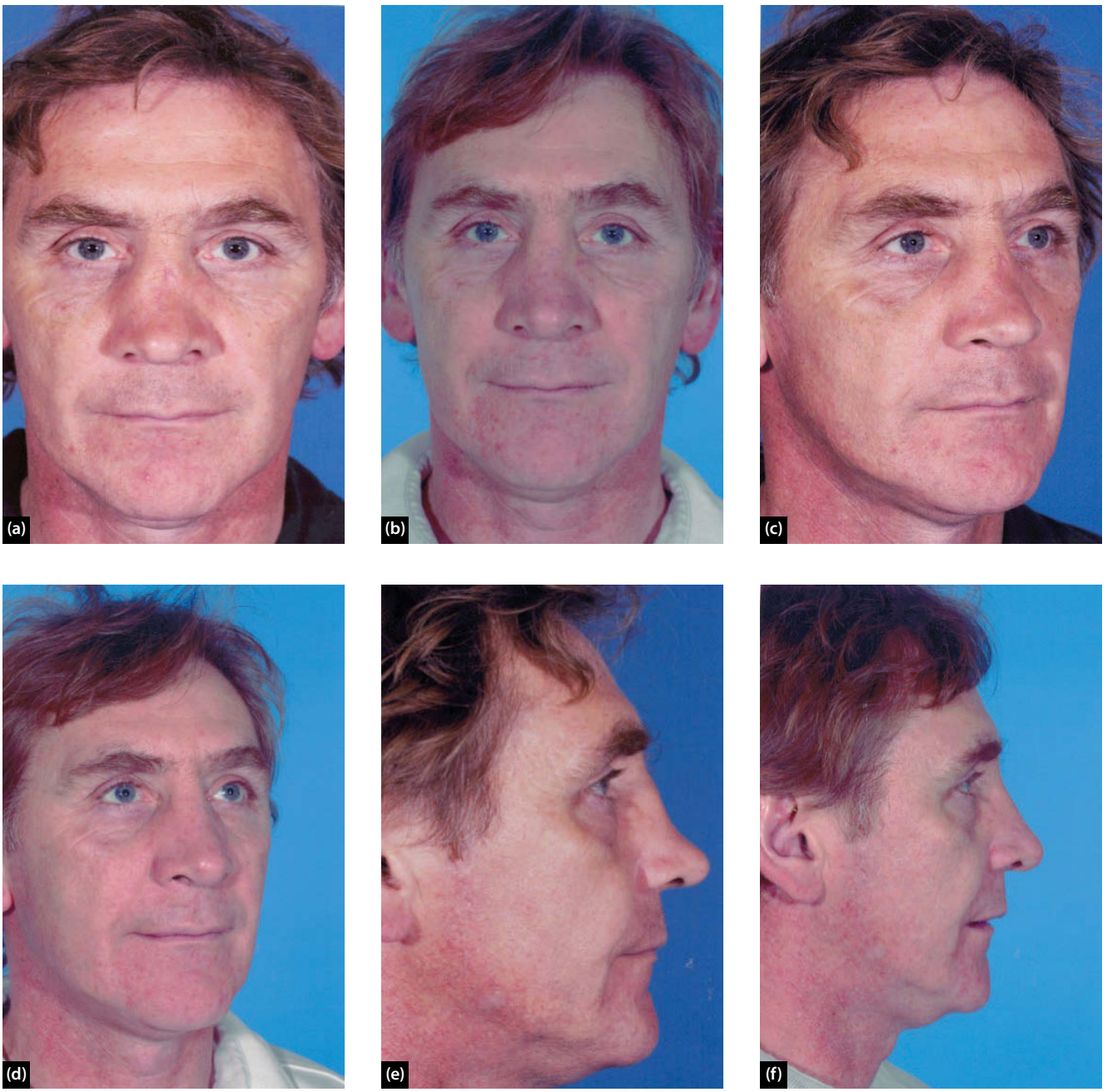


Figure 82.11 (a–f) Pre- and post-operative images of a patient undergoing secondary rhinoplasty with residual septal and ear cartilage harvest. Septal L-strut reconstruction with an onlay diced cartilage and fascia graft, columellar strut graft with mild tip deprojection, and medial and lateral osteotomies were performed.

Grafts can be used as a solid implant, with careful fashioning and chamfering of its edges to reduce the risk of post-operative visibility. These can be placed into a 'hand-in-glove' type pocket to avoid movement post-operatively but the open approach allows for graft stabilization with sutures accurately placed. The same principles apply also to placement of diced cartilage in fascia grafts (**Figure 82.12**) where suture fixation will ensure that the graft remains secure and will not move in the post-operative recovery period.

Cleft-lip nasal deformities

Rhinoplasty in a cleft-lip patient is challenging due to the limitation of the final post-operative result.[38] The severity of primary nasal deformities is directly related to the severity of the cleft lip. The nasal and vestibular skin as well as the cartilaginous and bony skeleton is affected. Cleft-lip nasal deformities can be classified into unilateral and bilateral and form a characteristic pattern.[35] The secondary, and hopefully definitive, nasal reconstruction should be performed using the external rhinoplasty technique in the presence of severe tip asymmetry. The use of conservative techniques allows the procedure to be performed before puberty. However, the surgeon has to weigh up the psychological and future nasal directional growth benefits against possible inhibition of mid-facial growth,[35, 36] although studies have questioned whether septal surgery via an external approach truly has an effect on future nasal and midface development.[37] A V–Y procedure to lengthen the columella is usually needed in bilateral cleft deformities, and this should be considered when placing the incision. A complete cleft will be associated with hypoplasia and retropositioning of the maxilla on the cleft side. If mild, a cartilaginous graft can be used for support in order to relocate the alar base; in severe cases, a maxillary advancement will be needed. The key to correcting tip asymmetry is a stable and symmetrical base formed by the columella strut or, perhaps better still, a septal extension graft (see **Figure 82.8**). The lower lateral cartilage on the cleft side must first be dissected free, after which it can be repositioned and sutured to the cartilaginous columella support (more anterocephalic).[35, 40] This does not alter the lateral alar base displacement. A Z-plasty to reposition and to counter-rotate the ala at the cleft side is often required.[35] Finally, a shield graft may be positioned, which further increases tip projection, enhances tip definition and camouflages minor tip asymmetries.[39]

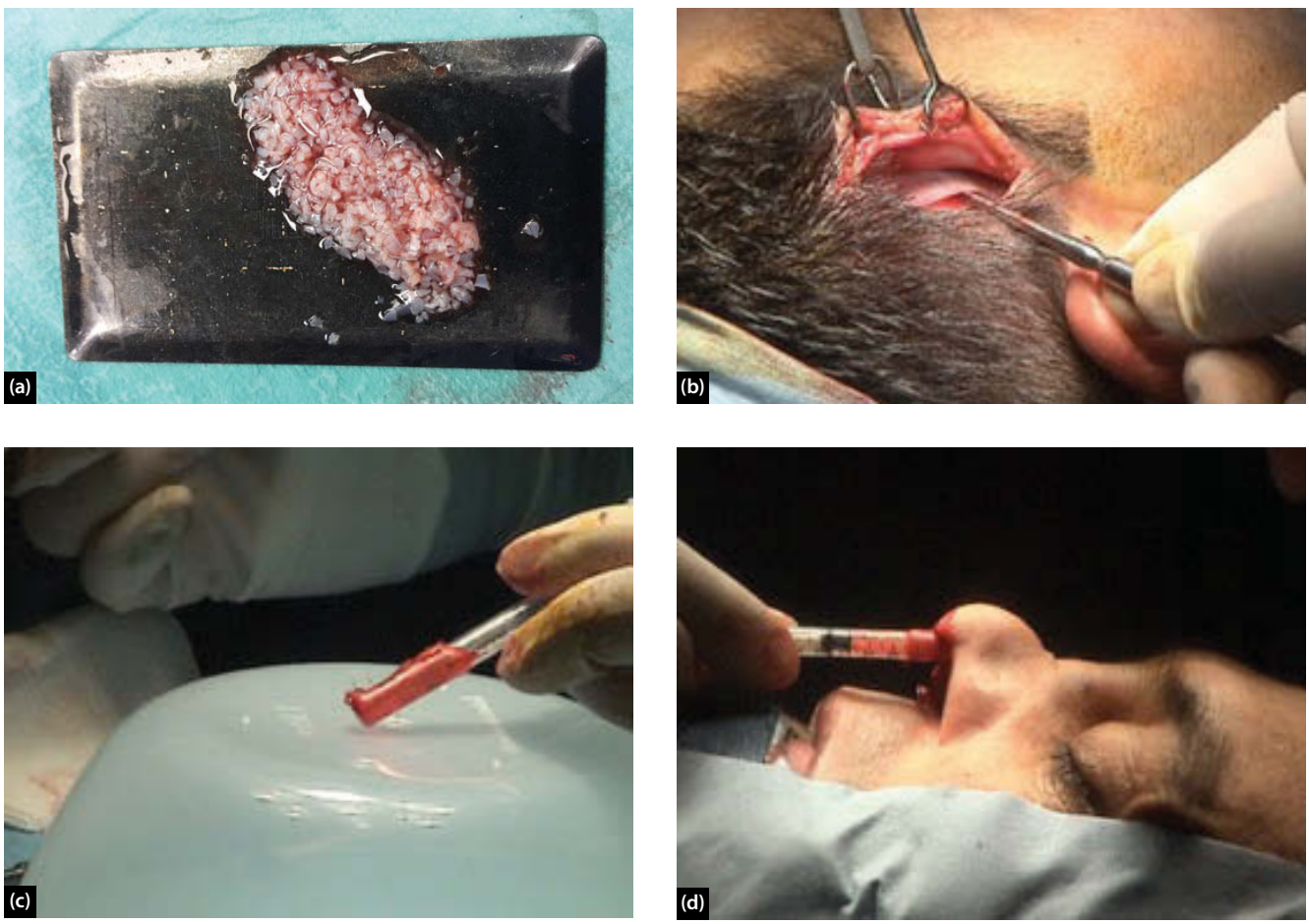


Figure 82.12 **(a)** Finely diced auricular cartilage. **(b)** Harvest of temporalis fascia. **(c)** Fascia wrapped around a 1 ml syringe. **(d)** Diced cartilage placed into syringe and injected with fascial wrapper onto dorsum.

Septal perforation repair

Contemporary techniques of septal perforation repair rely on mobilization of mucoperichondrial flaps to allow individual closure, usually with an interpositional graft. Such dissections are laborious and challenging and the external approach may be undoubtedly facilitating, particularly in the repair of large septal perforations.[8, 9] It allows unique exposure of the septum from both the cephalic and the caudal aspect and also aids any required conjunctive rhinoplasty. The septal flaps are then more easily released and advanced to allow for a tensionless closure, and suturing of the flaps is aided by the wide exposure.

Nasal dermoids

The poor cosmesis associated with a vertical midline scar required in total excision of a nasal dermoid may be avoided by use of the external rhinoplasty approach and its use has been advocated widely.[10] The dermoid can usually be dissected off the overlying skin although there may be a small of area of cutaneous resection required and, if particularly large, any excessive redundant skin may require resection.

CASE EXAMPLES

Figures 82.13 and **82.14** illustrate cases in which an external rhinoplasty approach was used to advantage for correction of specific deformities. The patient in **Figure 82.13** was a revision case in which there was need for significant grafting to allow improvement of both function and form. The open approach facilitated accurate diagnosis of the deformity and placement and suturing of the various grafts that were harvested from the residual septum and auricular region. The patient in **Figure 82.14** sought cosmetic

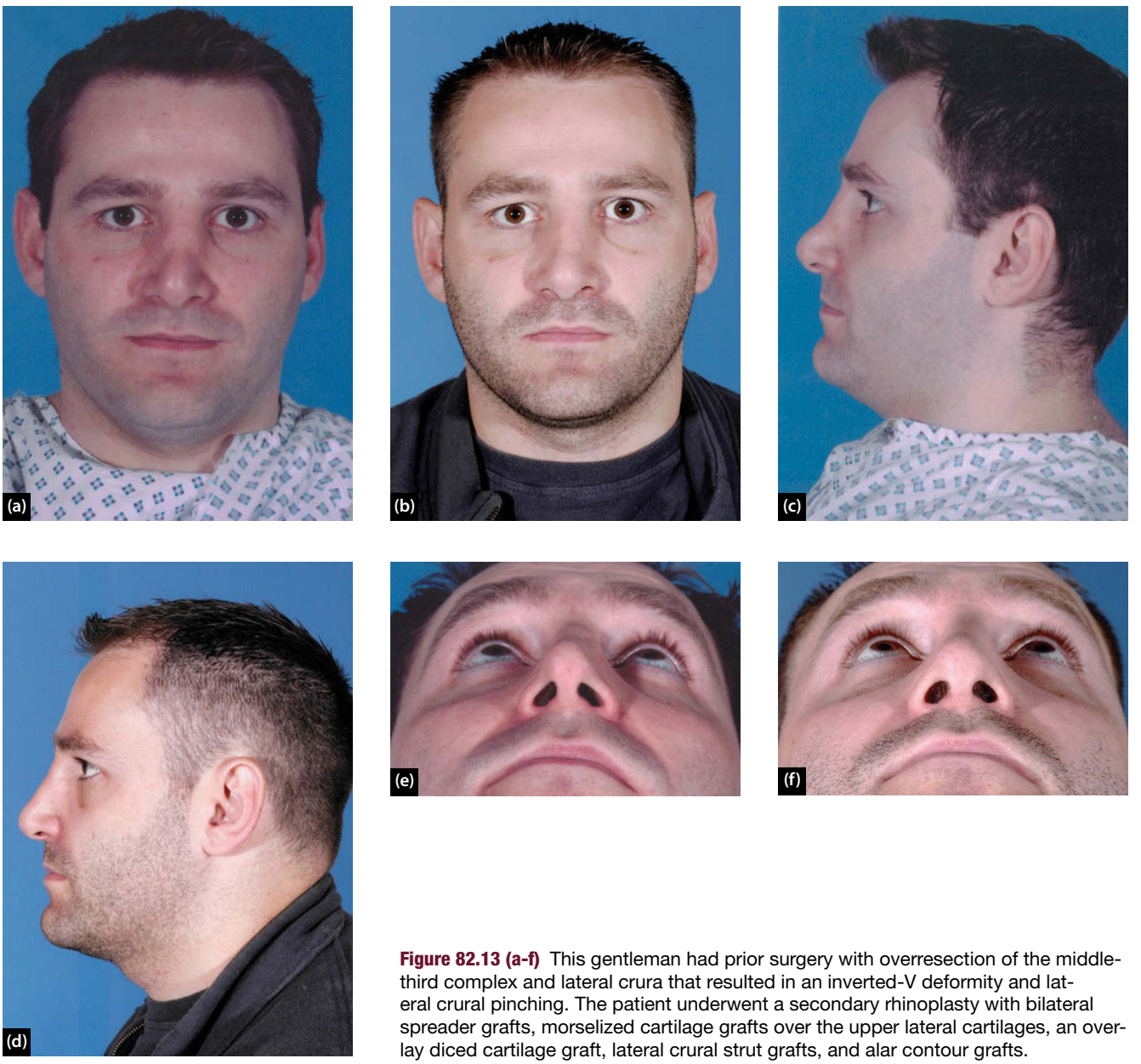


Figure 82.13 (a-f) This gentleman had prior surgery with overresection of the middle-third complex and lateral crura that resulted in an inverted-V deformity and lateral crural pinching. The patient underwent a secondary rhinoplasty with bilateral spreader grafts, morselized cartilage grafts over the upper lateral cartilages, an overlay diced cartilage graft, lateral crural strut grafts, and alar contour grafts.

Figure 82.14 (a-h) Pre- and post-operative photographs of a patient undergoing a reduction rhinoplasty. The patient had dorsal cartilaginous and bony reduction, insertion of bilateral but asymmetrical spreader grafts, medial and lateral osteotomies, tip rotation with a tongue-in-groove procedure, tip deprojection with a lateral crural overlay, and domal sutures.

improvement of the rather overprojected nose with reduction of the dorsal hump. Again the open approach allows simple placement of spreader grafts as well as the ability to use the tongue in groove and lateral crural overlay techniques effectively and precisely.

CONCLUSIONS

The external approach has proven to be a valuable part of the armamentarium of the rhinoplasty surgeon. Its unparalleled exposure and the ability to bimanually manipulate and handle underlying tissues gives a major advantage to endonasal techniques, particularly in more complex surgery, revision and post-traumatic deformity. It facilitates accurate resection and modelling of underlying bony and cartilaginous components and enables straightforward placement and suturing of graft material. Correct incision placement, dissection in the right surgical planes and meticulous suturing techniques prevent unnecessary sequelae of this approach, such as prolonged supratip oedema and aesthetically unacceptable transcolumellar scars. Relative disadvantages of increased operating time and difficulty of dorsal assessment are minor and should improve with the experience of the surgeon.

FUTURE RESEARCH

- ➤ There is much work being done presently with use of powered instrumentation, especially with the Piezoelectric devices.
- ➤ Popularity of powered instrumentation has grown in recent years but it will remain to be seen whether the additional extensive skin degloving required and the cost of the equipment will make these instruments a mainstay in the future.
- ➤ Additional research into powered instruments may shape future use of such devices.

KEY POINTS

- The external approach affords superior visualization of underlying deformities, allows bimanual handling of tissue and accurate placement of grafts and sutures.
- Modern techniques for tissue dissection planes and scar placement and suturing minimize the previously quoted disadvantages of this approach.
- The principle of limiting tissue dissection as much as possible remains and endonasal techniques may be employed in less complex cases.
- Structural grafting techniques to maintain long-term stability of the nose often necessitates an open approach.
- An appropriately placed broken line incision with meticulous closure allows for minimal visualization of the columellar scar with time.

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CHAPTER 83

REVISION RHINOPLASTY

Claudia Rudack and Gerhard Rettinger

Introduction 1161
Revision rates 1161
Classification and frequency of deformities requiring revision rhinoplasty 1162
Factors affecting prevention 1162
Treatment strategies 1164
Conclusion 1166
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SEARCH STRATEGY

Data in this chapter may be updated by searches of Embase, the Cochrane Library and PubMed using the keywords: secondary, revision, rhinoplasty.

INTRODUCTION

Rhinoplasty (in contrast to septorhinoplasty) focuses mainly on altering the appearance of the external nose for aesthetic reasons. In certain cases, for example in a tension nose or in alar insufficiency, rhinoplasty is performed to correct the nasal airways. A septorhinoplasty attempts to improve both the aesthetic appearance and the function of the nose. This combined procedure may add additional dynamics in the healing process and therefore revisions may be more common.[1] This chapter primarily deals with visible deformities after previous rhinoplasty, their types and frequencies, possible causes, their prevention and their correction. Unfavourable results may be the consequence of unpredictable healing, which is beyond the surgeon's control, and these are generally referred to as 'complications'. However, revisions may also be necessary because of an inadequate primary procedure, which is then termed a 'mistake'. In this situation, the patient usually blames the surgeon responsible for the ultimate outcome. For the surgeon, it is important to understand the difference between a complication and a mistake and to learn from revision surgery.[1]

The surgical procedures available for revision rhinoplasty are numerous[2–8] and are mostly based on the experience of the individual rhinoplasty surgeon. Because of this, only the more common techniques for the most frequent residual deformities will be discussed.

It is difficult to draw general conclusions from the literature. On one hand, reports on long-term results are very rare and most publications describe the number of revisions that are undertaken 1–2 years after primary surgery. It is possible that many problems that give rise to revisions may present much later. In addition, the patient population analyzed in an article will be non-homogeneous. The primary surgery can be performed by different surgeons with different experience and technical factors may contribute to post-rhinoplasty deformities. In addition, follow-up of patients operated on by a single surgeon may be incomplete. He or she may only see patients with minor deformities, who tend to return to the primary surgeon. Patients with major deformities, however, tend to seek an opinion from a second surgeon.[9] Comparing figures on types of post-operative deformities in different studies may also be of limited value. Noses, as well as surgical goals, may differ between countries and continents. What may be an acceptable result in one country may be an indication for revision rhinoplasty in another.

These factors do not facilitate the reporting of evidence-based data. This means that the figures presented can only represent a tendency and give support for a better understanding of the development of deformities after rhinoplasty, their prevention and revision techniques.

REVISION RATES

Most data from the literature describe revisions after aesthetic rhinoplasty, rarely for functional aesthetic rhinoplasty. This must therefore be taken into consideration when drawing any conclusions.

Reported revision rates are listed in **Table 83.1.** In general, a revision rate of 5–10% is to be expected.[14] Specialized surgeons will undertake more revisions because patients are more likely to be referred to them. In the large series by Parkes et al. of 1221 consecutive rhinoplasties,[14] the overall revision rate was approximately 14%. However, their own

TABLE 83.1 Revision rates after primary or multiple rhinoplasty

Author	Year	Total no. patients	Revision (patients %)
Klabunde et al.[10]	1964	300	30/10
Smith[11]	1967	221	27/12
McKinney et al.[12]	1981	200	24/12
Swanepol et al.[13]	1981	882	63/7.1
*Kamer et al.[9]	1988	638	67/10.5
Parkes et al.14	1992	1221	170/13.9
*Vuyk et al.[15]	2000	480	110/23
Costantian et al.[17]	2000	-	150
*Bracaglia et al.[18]	2005	-	311
Foda et al.[19]	2005	50	50
Rettinger et al.[2]	2007	502	184

*No consecutive series of primary or multiple rhinoplasties.

revision rate was only 5.3%. The frequency of having more than one revision lies between 20% and 23% of all revision cases.[9, 14, 15] Revision rhinoplasty is more commonly performed in females, with rates of 60–80%.[14, 15] In a series of 200 consecutive rhinoplasties undertaken by a single surgeon, 12% had revisions. Of these, more women (14%) than men (9%) were dissatisfied with the surgical result.[12] In contrast to these figures, the rate of dissatisfied patients in a population of 1062 patients who had undergone rhinoplasty and who then completed a questionnaire afterwards (468 responders) was higher among male patients (12.8%) than among female patients (4.6%).[16] Interestingly, a study cohort comprising 175 842 participants who underwent septorhinoplasty procedures showed an overall revision rate for any septorhinoplasty procedure of 3.3% (5775 of 175 842) (99% CI, 3.2–3.4%). After separating the patients into primary septorhinoplasty and secondary septorhinoplasty groups, the primary group had an overall revision rate of 3.1% (5389 of 172 324), while the secondary group had an overall revision rate of 11.0% (386 of 3518). Patient characteristics associated with an increased rate of revision include younger age (5.9% [633 of 10 727]), female sex (3.8% [2536 of 67 397]), a history of anxiety (3.9% [168 of 4350]) or autoimmune disease (4.4% [57 of 1286]), and surgery for cosmetic (7.9% [340 of 4289]) or congenital nasal deformities (8.9% [208 of 2334]).[20]

CLASSIFICATION AND FREQUENCY OF DEFORMITIES REQUIRING REVISION RHINOPLASTY

A systematic approach to revision rhinoplasty may be based on the type of surgical procedure needed or the type of the deformity to be corrected. Webster defined five categories of revision:[21]

- revision uncertain or unnecessary
- revision with skeletal reduction
- revision with skeletal augmentation
- external soft-tissue removal required
- revision in congenital anomalies, major trauma, etc.

Other authors have described the location of the deformity (**Table 83.2**). Cohen lists eight different groups of external abnormalities and also includes functional disturbances.[22] Stucker, however, divides the nose into thirds: the upper (bony) third, the middle cartilaginous third and the lower third.[23] These parts can be further subdivided (see **Table 83.2**).[24] Kamer and McQuown[9] include the severity of the deformity. They distinguished between major deformities, such as saddling, midnasal asymmetry, pollybeak, retracted ala and columella, and minor deformities, which included tip-bossae, wide nasal base, hanging columella, irregular or high nasal dorsum and acute nasolabial angle.

The frequency of different deformities as reported by the eight authors above is listed in **Table 83.2.** The risk for residual deformities increases from the upper to the lower third of the nose. Most frequently, dropping tips and pollybeaks were found. Uncorrected broad nasal tips and irregularities of the nasal dorsum are also relatively frequent causes of revision.

These figures demonstrate the particular importance of the nasal tip support and its dynamics in the healing process. As the supratip pollybeak and dropping of the tip are frequently combined, the rhinoplasty surgeon has to put special emphasis on maintaining adequate tip protection, as well as protection when approaching and mobilizing the nasal infrastructure. The common deformities that can occur following rhinoplasty are listed below in order of frequency of occurrence:

1. pollybeaks
2. dropping tips
3. uncorrected broad nasal tips
4. irregularities of the nasal dorsum.

FACTORS AFFECTING PREVENTION

Proper patient selection can influence the surgical result. For example, rhinoplasty with advancing age can be associated with the patient's own expectations and motivations. This may influence the surgeon to do more than is adequate. The result can be an overzealous rhinoplasty.

Safian[25] has described three basic rules to prevent any problems developing after rhinoplasty:

- Never change the normal basic anatomy or the anatomic relationships of the nose and never totally remove a component.
- Never allow the skin and lining membrane to meet or be left in contact.
- Never destroy nasal cartilage.

The revision concepts of Sheen[26] are based on a proper pre-operative diagnosis, limited dissection, use of

TABLE 83.2 Classification and frequency of post-rhinoplasty deformities (% of revisions)

	Parkes et al.[14]	Vuyk et al.[15]	Kamer and McQuown[9]	McKinney and Cook[12]	Constantian[17]	Foda[19]	Bracaglia et al.[18]	Rettinger[2]
Total/revisions	1221/170	480/110	697/126	200/24	150	50	311	184/502
Upper third	41	79						
Excessive dorsal removal/low dorsum/saddle	24	32	16		93	44	70	44
High dorsum	4	19						3
Dorsal irregularity	16	2	17	21		54		
Wide bony pyramid	2	13				42		20
Shifted graft/asymmetry	1	3	6				80	45
Middle third	63	106					40	
Pollybeak/high dorsum	33	40	56	8		64	50	21
Cartilaginous saddle	14	21						
Pinched/narrow cartilaginous dorsum	8	5						2
Uneven/wide cartilaginous dorsum	10	14	15					
Asymmetric cartilaginous dorsum		23	16					4
Lower third	94	181						
Tip deformities								
Overprojected tip		5						
Underprojected (dropping) tip	4	32			80			
Over-rotated tip (short dorsum)						42		10
Under-rotated (dependent) tip	10	17						53
Deviated tip		1						
Broad/amorphous tip	8	18		46				
Narrow/pinched tip	0.6	5						
Asymmetric tip/bossae	26	30	22					
Alar deformities								
Alar retraction	12	7	11					
Wide alar base		5	8				10	
Columella deformities								
Hanging columella	17	6	13				20	5
Retracted columella	4	11	9					5
Acute nasolabial angle	8	16	4					

exclusively autogenous graft material when required and a well-defined pre-operative plan.

Webster's guidelines include an adequate interval before revision (normally 1 year). This acknowledges the effects of scar tissue and recognizes the differences between underdone and overdone noses, the use of autogenous tissue when dealing with the lining of the nose and the need to develop the aesthetic and reconstructive skills required for revision rhinoplasty.[21]

Constantian[17] reviewed 150 consecutive secondary rhinoplasties in a retrospective study to test the hypothesis that specific anatomic variants predispose to unfavourable rhinoplasty results. He defined four pre-operative variants and compared their incidence with a primary rhinoplasty group. The following conditions were found more frequently in revision patients:

- low radix, low dorsum (93%)
- narrow middle vault (87%)
- inadequate tip projection (80%)
- alar cartilage malposition (42%).

The 'triad' of the first three points was most common (40%), so patients with the combination of these deformities are at a higher risk for revision surgery (**Figure 83.1**).

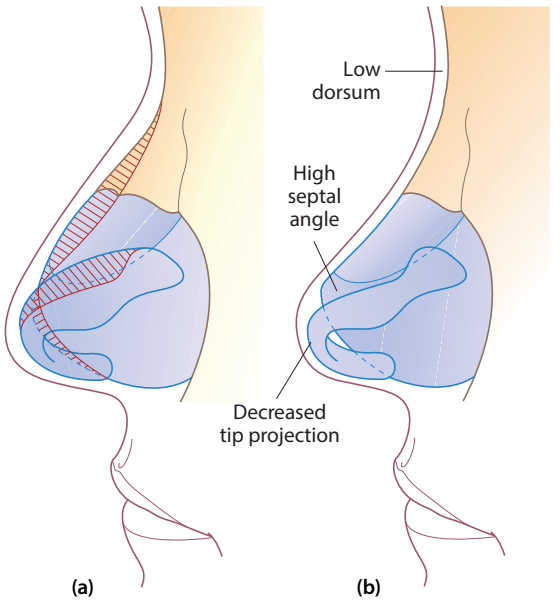

Figure 83.1 Predisposing factors for pollybeak deformity and profile changes: low radix, high dorsum, low tip projection. (a) Hump removal and resections of caudal septal end and lateral crura are marked; **(b)** post-operative result.

TREATMENT STRATEGIES

As already mentioned, techniques for revisions described in the literature are mainly based on the personal experience and preferences of the surgeon. Therefore, only principles and concepts for the most frequent causes for revisions are described here.

Pollybeak deformity

Although there may be cases with a soft-tissue thickening in the supratip area post-operatively, the majority of pollybeak deformities are caused by two effects (see **Figure 83.1**):

- dropping of the nasal tip (loss of tip projection and protection)
- an absolute or relative high septal angle.

The pollybeak deformity develops within months after surgery and this is because of the surgically induced loss of tip support mechanisms.[27] The end result will be a relatively high cartilaginous dorsum in relation to the position of the tip that is sometimes combined with a relatively low bony dorsum (**Figure 83.1**). In principle, there are three options for reconstruction:

- increase of tip projection
- reduction of cartilaginous nasal dorsum
- a combination of both.

The most reliable technique to increase tip projection and protection is a columella cartilage strut with fixation of the medial crura using an external approach (**Figure 83.2**).[28] If the nasal tip is still in a reasonable position after primary surgery, further reduction of the cartilaginous dorsum may be sufficient. In severe cases, both structures must

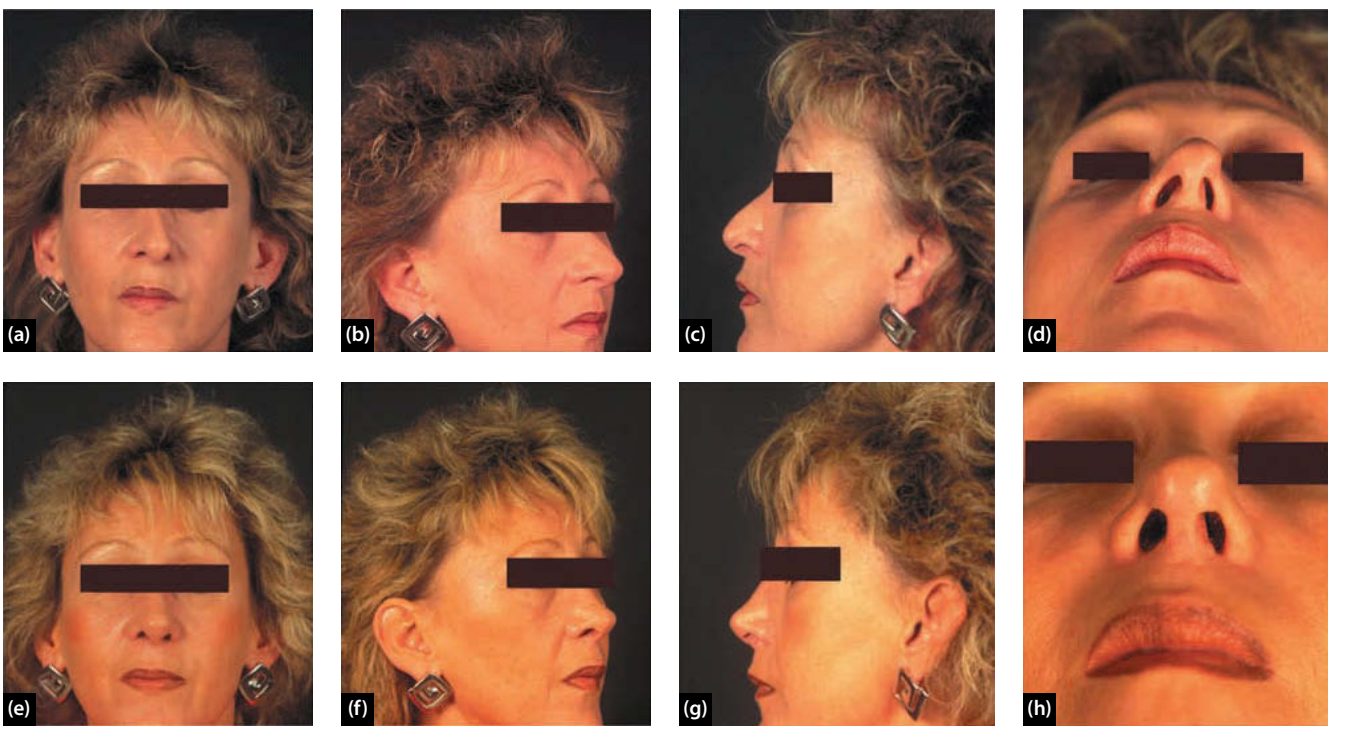

Figure 83.2 Deviation of the nasal dorsum and pollybeak deformity after three previous rhinoplasties. Low radix, narrow middle vault and alar cartilage malposition after dome division on the left side **(a–d)**. Revision via open approach (fourth operation): septal and columella reconstruction with autogenous rib graft, radix augmentation and spreader grafts. Reconstruction of left alar cartilage **(e–h)**.

be addressed. In principle, the dorsum must be adapted to the definite position of the nasal tip.

Irregularities of the nasal dorsum

These irregularities become visible after hump removal, especially in thin-skinned patients with prominent nose syndrome (tension nose). Very often they are found at the K-area where the nasal bones overlap the triangular cartilages. While minor bony ridges can be easily rasped, this technique is not possible for a cartilaginous deformity. The surface of the cartilage must be made smooth with scissors or a knife. In very thin skin, camouflage can be an excellent option. After further reduction of the nasal dorsum, tissue (mainly autogenous) is used to cover the whole distance from the radix to the septal angle. A crushed septal cartilage strut with delicate smooth edges is preferred (**Figure 83.3**). New insights came from using the technique refining the nasal dorsum with free diced cartilage.[29, 30] Ear cartilage and temporalis fascia are somewhat less suitable. Alloplasts, such as Gore-Tex, may be helpful in selected cases.

Crushed cartilage and free diced cartilage can be very useful to fill small depressions lateral to the nasal dorsum that give the appearance of a deviated nose. This camouflage is very often more effective than revision surgery with osteotomies.

Columella deformities

The acute nasolabial angle with retraction of the columella is often associated with a wide columella base. This can be caused by an over-resection or malposition of the caudal septal end, resection of the anterior nasal spine or creation of a columella pocket between the medial crura which allows the soft tissues to slide posteriorly. It can also be the result of an 'endorotation' of the nasal septum after mobilization during septoplasty.[31] The distance between columellar skin and caudal septum can be increased by inserting a cartilage strut after closing the space between the medial crura footplates with a non-resorbable 'U' suture. In case of a malposition of the septal cartilage after septoplasty, it can be repositioned ('exorotation') and fixed to the anterior nasal spine (**Figure 83.4**).

Overshortened noses

Although this deformity is not listed as a frequent cause for revision in Table 83.2, it is often cited in medicolegal cases. The wide open nasolabial angle in an over-rotated tip is extremely unpleasant and disturbing aesthetically. Very often, the surgeon's pre-operative analysis was inadequate. In a relatively long nose with a moderate hump, the decision was made to remove the hump and shorten the nose because it appeared even longer after hump removal (**Figure 83.5a**). Typical manoeuvres to shorten the nose include:

- resection of a triangular part from the caudal septum (with or without resections from the membranous septum, with or without columella pocket)
- resection of the cephalic margins of the lateral crura (with or without interrupted remaining cartilage strip)

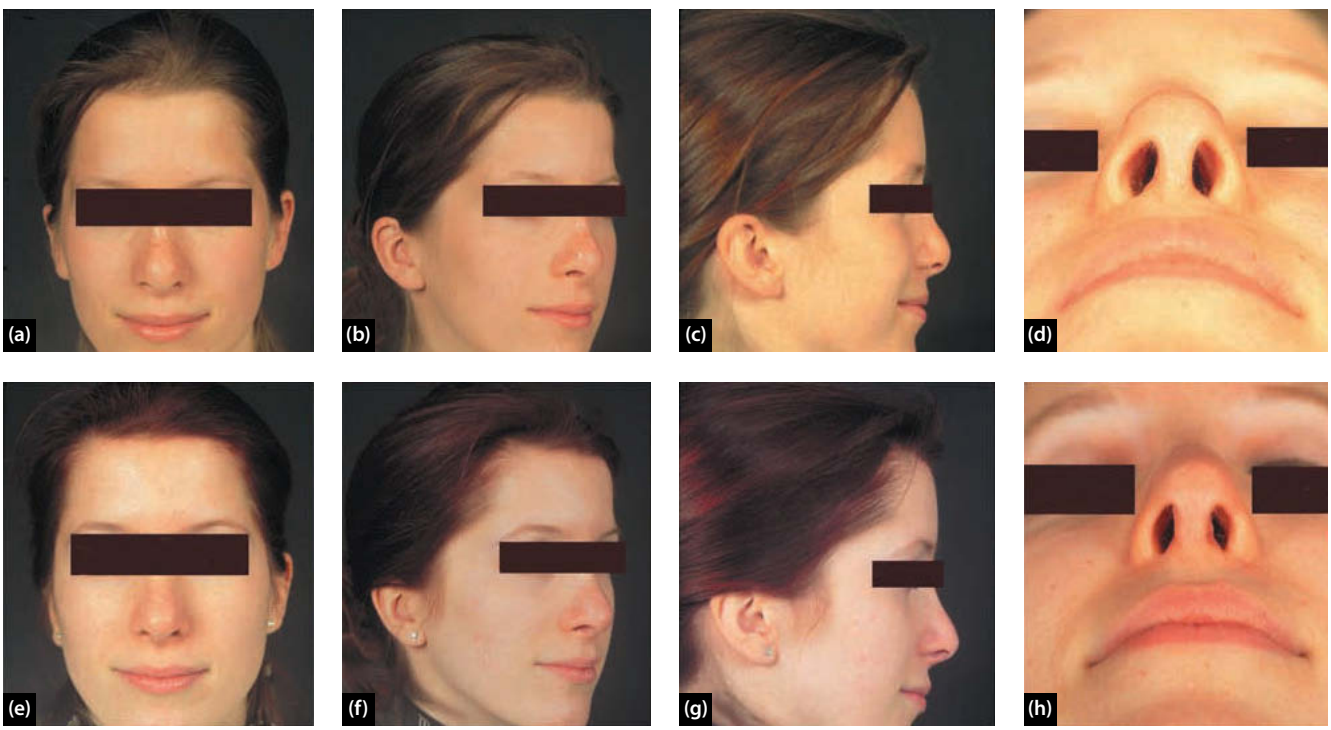

Figure 83.3 Narrow bony vault, irregularities of the dorsum and amorphous tip with pollybeak deformity after hump removal and tip surgery (delivery approach) (a–d). Revision via open approach: septal cartilage strut to the nasal dorsum, tip-suturing technique and tip graft **(e–h)**.

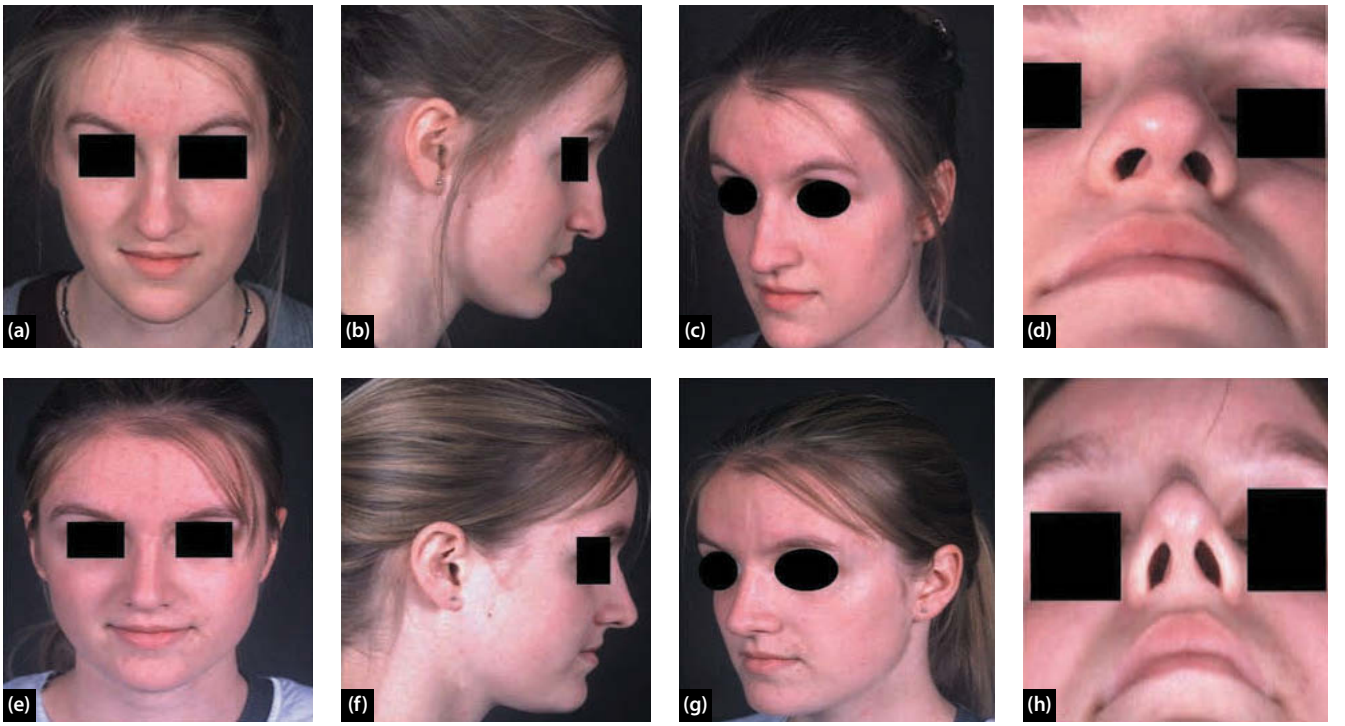

Figure 83.4 Sagging of the cartilaginous dorsum (bony pseudohump), loss of tip support and retracted columella after septoplasty and partial resection of the causal septal end (a–d). Reconstruction of the caudal septal end and repositioning of the septal cartilage. No removal of the pseudohump or nasal dorsal grafts **(e–h)**.

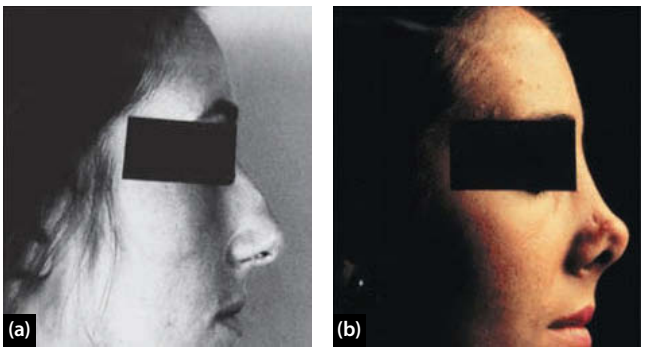

Figure 83.5 Overshortened nose and nasal base irregularities after reduction rhinoplasty. (a) Pre-operative analysis with moderate hump and nasolabial angle about 110°. Post-operative extremely open nasolabial angle and alar retractions after partial resections of alar cartilages and caudal septum **(b)**.

- sometimes resection of the inferior border of the triangular cartilages.

If the surgeon does not respect the nasolabial angle which was already close to 110 degrees pre-operatively (**Figure 83.5a**), then the result, if too much cartilage or even vestibular skin were removed from the lateral crura, is a foreshortened nose (**Figure 83.5b**).

Revision is very difficult in extreme cases. Normally, the limiting factor is not the nasal skin, which can be stretched if it is not too scarred. The problem comes with deficiencies in the inner lining, which is much more rigid than the external skin and can limit the lengthening of the dorsum and downward rotation of the tip. To reconstruct the retracted columella base can be impossible, since too many scars prevent the mobilization of the soft-tissue envelope. The new position of the soft tissues and the infrastructure must be secured by grafts. They can be applied following five principles:[32]

- flying buttress graft (spreader graft and columella graft) (**Figure 83.6**)
- caudal septal graft
- tip grafts
- radix grafts
- interposition grafts (between the upper and lower lateral cartilages).

Depending on the initial problem, revision surgery in an overshortened nose can improve the situation, but perfect reconstruction of all the deformities is uncommon (**Figure 83.7**). This means prevention is of utmost importance and the nasolabial angle should be checked carefully when tip rotation and shortening of the nose is planned.

CONCLUSION

The expected revision rate following primary rhinoplasty should be between 5% and 10%. Factors predisposing to

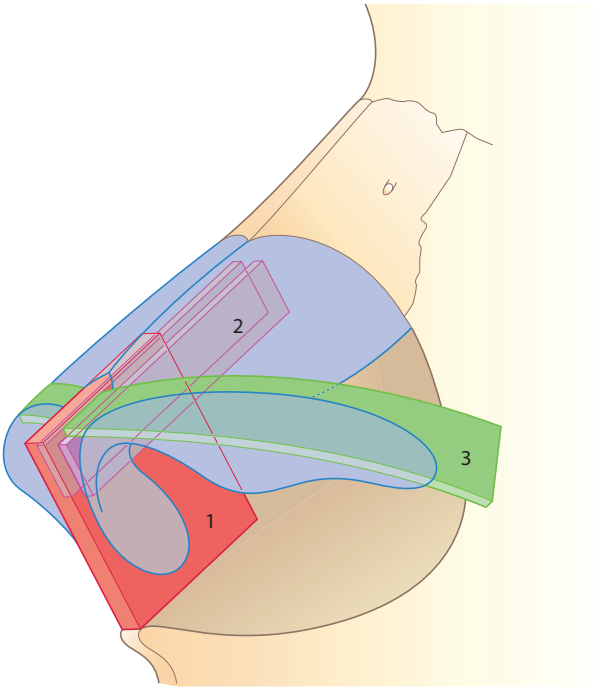

Figure 83.6 Grafts to lengthen an overshortened nose: combined septum and columella graft for downward projection of the columella (1); spreader grafts between the upper lateral cartilages to secure the length of the nasal dorsum (2); interposition grafts between upper and lower lateral cartilages for inferior projection of the alar rim (3).

revisions are thin skin, a low radix, the narrow middle vault and reduced tip projection. The most frequent deformities that may develop in these patients are the pollybeak deformity and irregularities of the nasal dorsum. Another frequent unfavourable outcome, especially of septoplasty or septorhinoplasty, is the cartilaginous saddle nose

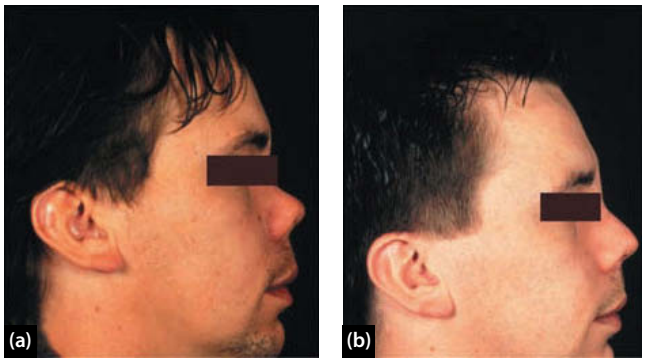

Figure 83.7 Short nasal dorsum, low radix and retraction of columella base as a result of reduction rhinoplasty (a). Reconstruction with autogenous rib grafts. The nasal skin allows lengthening of the nasal dorsum, but downward projection of the columella base is limited because of the inner lining **(b)**.

with decreased tip projection and retracted columella. Overshortened noses tend to become medicolegal cases.

Although prevention during primary surgery can minimize the risk for post-operative sequelae, a planned second stage may be advocated and discussed with the patient in advance. However, the surgeon and patient must be aware that perfection is not always possible and revisions (especially when multiple) have a smaller chance of achieving the optimum result when compared with primary surgery.

The next generation of rhinoplasty surgeons and their patients will benefit from our experience. This experience, however, should not be based solely on personal opinion and the results of 'learning by doing'. We need more systematic evaluation and controlled studies than those available and cited in this chapter. All risk factors should be defined and prevention strategies developed, taking into account the outcome not only after 1–2 years but also after 10 years or more.

BEST CLINICAL PRACTICE

- ✓ Definition of standard surgical techniques for each nose deformity and anatomy for each surgeon.
- ✓ A systematic procedure for follow-up after one or more years is required to analyze post-operative results.
- ✓ Residual deformities or the development of other undesired sequelae should be clearly linked to the individual anatomy or the surgical technique used.

FUTURE RESEARCH

- ➤ Systematic evaluation of new surgical techniques (i.e. grafts, osteotomy) in rhinoplasty by specialized rhinoplasty centres before broad application in patients.
- ➤ Outcome research for evidence of nasal resistence measurements pre- and post-operatively.
- ➤ Development and establishment of specialized training centre and skills labs for rhinoplasty.

KEY POINTS

- Revision rates are between 5% and 10%.
- The most frequent deformities are pollybeak, dropping tip, broad tip and irregularities of nasal dorsum.
- Predisposing factors are low radix, narrow middle vault and inadequate tip projection.
- Patients with overshortened noses tend to take legal action.

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CHAPTER 84

AESTHETIC DORSAL REDUCTION RHINOPLASTY

Julian M. Rowe-Jones

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Indications and aims 1169
Contraindications 1170
Techniques and avoidance of complications 1172
Outcome assessment and the future 1174
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SEARCH STRATEGY

Data in this chapter may be updated by a Medline search using the keywords: reduction and rhinoplasty. The author's own bibliography and library were also referred to. No references were found in the Cochrane database under rhinoplasty.

INTRODUCTION

The term 'reduction rhinoplasty' implies a formal, standardized approach to aesthetic nasal surgery. This concept has been inherited from Joseph[1, 2] and has been based for many years upon removing tissue from key anatomical nasal structures. His technique for cosmetic nasal surgery was developed in response to a case-mix predominantly comprising patients with abnormally large noses that invited ridicule.[3]

The classic Joseph reduction rhinoplasty is characteristically performed through intercartilaginous and full-length transfixion incisions and involves the following stages:[4]

- cephalic to caudal Joseph's saw bony hump reduction
- lowering of the cartilaginous dorsum
- triangular shortening of the caudal edge of the nasal septum
- use of a saw for lateral osteotomies with infracture
- alar cartilage cephalic rim reduction.

This generic approach to the oversized nose has been replaced by one that seeks to develop individual operative plans for each patient, tailored to careful pre-operative analysis of the anatomical variants. Sheen has championed a balanced approach to rhinoplasty which may involve augmentation of some areas of the nose as well as reduction of others.[4, 5] No longer in every patient is the tip reduced and then the dorsum lowered to fit the tip. Development of new rhinoplasty techniques has enabled surgeons to achieve the ideal tip position in relation to the ideal nasion height and position. These two landmarks then dictate the ideal height for the dorsum.[6]

The reduction rhinoplasty is still effective in selected cases, either in part or in whole. However, it should not be employed routinely in all oversized noses or in all patients with abnormal dorsal convexity related to tip–dorsum disproportion. In light of increasing patient expectation and the increasing attention paid to detail around every component of lateral profileplasty, this chapter will focus and reflect on the aesthetic dorsal reduction component of reduction rhinoplasty alone.

INDICATIONS AND AIMS

Aesthetic dorsal reduction rhinoplasty is indicated for the patient with an overprojected nasal dorsum relative to the nasion and/or the tip, resulting in a convex lateral dorsal profile. This dorsal convexity will be accentuated if the nasal tip is underprojected in relation to the nasion or vice versa (**Figure 84.1**). In the ideal nose the ideal nasion should project 10–13 cm from the anterior corneal plane. The ideal position of the nasal tip in females will be found at a point that intersects a line drawn from the ideal nasion at 34 degrees to the vertical facial plane, with a line drawn from the alar crease at 105 degrees to the vertical facial plane. In males the angles are 36 degrees and 95 degrees respectively. Oversized or cephalically malpositioned alar cartilages may contribute to supratip fullness and convexity. This chapter will not address techniques to correct these deformities.

Figure 84.1 (a–c) Pre-operative and **(d–f)** post-operative reduction rhinoplasty views with 12-month follow. Open approach. Composite dorsal reduction. Endonasal low-to-high lateral osteotomies and medial oblique osteotomies. Right spreader graft. Left autospreader graft. 2 mm cephalic trimes of the paradomal lateral crura. Bilateral dome creation sutures, a dome equalization suture and two tip position sutures.

Surgery to correct underprojection of the nasion and/or nasal tip which may contribute to lateral profile convexity will also not be presented in this chapter.

The aim of reduction rhinoplasty is a strong nasal dorsum in the lateral profile, which relates to the ideal nasion height. The tip-defining point should be projecting just above the dorsal line to create a supratip break, although in males the tip position may be on a straight line with the dorsum.[7] The aim is for a non-operated appearance with a 'handsome and patrician' look[8] and a high, strong dorsum.[9] Furthermore, achieving an attractive lateral dorsal profile with dorsal reduction must not result in loss of normal aesthetic dorsal lines. Normal nasal function must also be preserved.

CONTRAINDICATIONS

In the rare instance that both the nasion and the tip are underprojected, dorsal reduction may be contraindicated and surgical planning should consider radix augmentation and tip projection. When determining whether to reduce

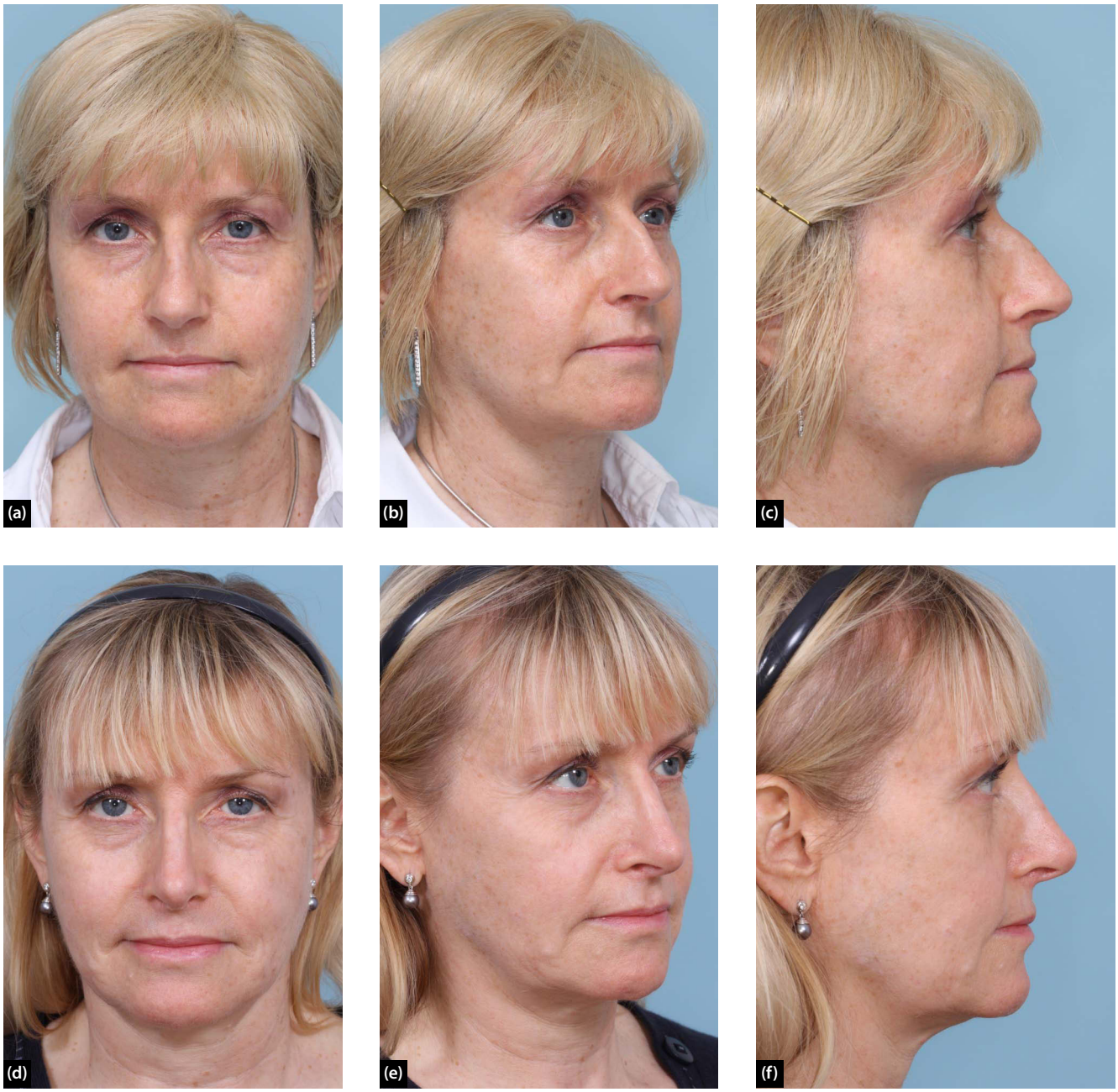


Figure 84.2 (a–c) Pre-operative and **(d–f)** post-operative reduction rhinoplasty views with 15-month follow. Open approach. Composite dorsal reduction. Percutaneous low-to-low lateral and superior transverse and endonasal medial osteotomies. Bilateral spreader grafts. Deep temporalis fascia ball and apron graft inserted to augment the radix and to cover the upper dorsum and K area. The lateral crura were trimmed to leave intact 6 mm strips. Bilateral dome creation sutures, an intermediate crural suture and a dome equalization suture of 5/0 PDS were inserted.

the nasal dorsum and, if so, by how much, analysis must consider projection at the radix, the rhinion and the tip. The degree of hump reduction may need to be modified and balanced with radix augmentation (**Figure 84.2**) and techniques to increase tip projection.

Reduction of the dorsum to fit an underprojected tip will result in an unnatural, over-resected nose, which appears flat and broad in the frontal view and lacks height in the lateral profile. Dorsal reduction in these patients alone would be unlikely ever to achieve an aesthetic lateral profile in which the tip projects above the dorsal line. This is especially relevant in thick-skinned patients when skin elasticity and shrink are limited.

Just as a hump may only be a relative hump[5] due to underprojection of the tip, so pseudohumps may be apparent in patients with supratip depression characteristic of a saddle nose. Often saddle noses also have an underprojected tip, which further contributes to the appearance of a bony dorsal pseudohump. In such circumstances a natural dorsum is created by augmentation rather than reduction. If cartilaginous dorsal reconstruction is not performed and hump reduction alone is, dorsal aesthetic

lines in the frontal view will not be created and the nose will look flattened.

The same is often true in revision rhinoplasty for the soft-tissue pollybeak deformity. This results from primary over-resection of bony and cartilaginous dorsum in the thick-skinned patient and is exacerbated by techniques that also deproject the tip. Supratip dorsal reduction will achieve very little improvement and may exacerbate the problem by removing structural support for the skin.

Dorsal reduction must be very carefully considered and discussed with the patient who is happy with the shape of their nose but considers it too large for their face. Global reduction of the nose is required in such cases. Such surgery is complex and expects a lot from the skin with regard to shrinkage.

The overprojected radix in cases of dorsal convexity presents an anatomical area for which reduction may be contraindicated. A soft-tissue response of 25% reduction relative to skeletal resection has been demonstrated at the nasion.[10] It may therefore be more predictable to match the tip and dorsum to the nasion in these cases than to attempt aggressive nasion and dorsal reduction.

In all patients considering aesthetic rhinoplasty analysis must include detailed assessment to diagnose psychiatric disorders and personality types and traits that are associated with a high likelihood of surgery not meeting their physical or psychological expectations or of the patient not accepting or understanding unpredicatability.[11]

TECHNIQUES AND AVOIDANCE OF COMPLICATIONS

The patient is positioned in the reverse Trendelenburg with approximately 30 degrees of head up. The nasal mucosa is prepared topically with neurosurgical patties soaked in 1:1000 adrenaline solution and 5% lidocaine hydrochloride with 0.5% phenylephrine hydrochloride spray. Infiltration is performed with 2–4 mL of 2% lignocaine with 1:80000 adrenaline using a long, 27 gauge needle. The author most often uses an open approach. Infiltration is performed along the caudal end of the quadrilateral cartilage into the membranous septum and then deep to the perichondrium, particularly anteriorly and along the dorsal quadrilateral cartilage. Endonasally, infiltration is performed medial and lateral to the frontal process of the maxilla along the line of the lateral osteotomies, with the needle immediately adjacent to periosteum. Minimal infiltration is then placed laterally along the dorsum each side to avoid disguising the hump. Intradermal blebs of infiltration are raised along the incision lines and then injection is deep to the superficial musculoaponeurotic layer over the nasal skeleton that is to be exposed. The infiltration should be left for at least 10 minutes prior to surgery. During dissection, further infiltration is placed in the dissection planes, ideally subperichondrial and subperiosteal.

Surgery can be performed for dorsal reduction using a closed or open approach. Both must preserve tip projection when this is normal pre-operatively. An upper transfixion incision which avoids disrupting the relationship of the medial crural footplates to the quadrilateral cartilage and intercartilaginous incisions are used for the closed approach. When an open approach is chosen, the tip cartilages are not routinely separated for septal access. Their attachment to each other and the caudal septum is preserved. A hemitransfixion incision is used prior to opening the nose to access the septum. A superior submucoperichondrial tunnel is elevated bilaterally to expose the dorsal quadrilateral cartilage and adjacent upper lateral cartilages and the dorsal ethmoid plate deep to the nasal bones. If septal surgery is required or a septal cartilage graft is needed, the tunnels can be extended later in the procedure, after dorsal reduction and osteotomies. The author prefers to perform surgery in this sequence, with dorsal reduction and osteotomies preceding septal surgery. In this way the stability of the nose, particularly the keystone area, is best assessed after bone removal and fracture, which carry the greatest level of unpredictable disruption. This assessment of stability informs surgical decision-making with regard to septal procedures which could further destabilize the nasal keystone area.

If the open approach is chosen, three-way countertraction of the columella flap, alar rim and intermediate crus dome facilitates subperichondrial dissection of the lower lateral cartilages. In the midline the anterior septal angle is identified and subperichondrial dissection aided by infiltration, and hydrodissection proceeds along the cartilaginous dorsum. It is important to ensure that the anterior septal angle is well demonstrated so that the entire length of the nasal dorsum to the caudal limit of the hump to be removed is visualized. From the midline, subperichondrial dissection is continued laterally over the upper lateral cartilages. Perichondrial attachments in the scroll area may be adherent to underlying mucosa and the overlapping upper and lower lateral cartilages. Elevation is difficult here. This area is often also vascular. Good exposure of the upper lateral cartilages and their release from the superficial musculoaponeurotic system (SMAS) and perichondrium are necessary to facilitate precise medial edge resection, mobility and accurate reconstruction of the mid third later in the procedure.

At the pyriform aperture, sharp dissection is required to enter the subperiosteal plane over the bony dorsum. Lateral dissection over the bone should occur only as far as is required for bone removal. Maintaining skin and soft-tissue attachments to the majority of the frontal process of the maxilla minimizes the risk of excess medial movement after osteotomies.

The author prefers component dorsal reduction.[12] As described by Daniel,[13] the author prefers to begin reduction with bone removal. Incremental rasping is performed to uncap and leave intact the underlying cartilaginous upper lateral cartilages and their contiguous septal quadrilateral cartilage. The rasp is more predictable than an osteotome and graded rasps enable a graded reduction. The preserved upper lateral cartilages are then released flush from the septum in the midline with scissors or a 15 blade and the quadrilateral cartilage is incrementally reduced with an 11 blade. Rohrich[12] performs upper lateral cartilage release and incremental quadrilateral cartilage reduction prior to bone removal. Powered burrs,

rasps and blades may be used for bone reduction and may provide greater control and finesse.[14, 15] A decision then has to be made as to whether to trim the medial margins of the upper laterals incrementally to allow them to sit against the quadrilateral cartilage when retraction on the skin is released. The upper lateral cartilages tend to drop inferomedially when released from the quadrilateral cartilage. If resection is performed, it must therefore be conservative and also incremental. Daniel[13] terms release of the upper laterals and then incremental resection of the dorsal septum and upper laterals individually a 'vertical split-hump reduction'. He draws attention to the appreciation that excision of the dorsal septum lowers dorsal height while excision of the upper lateral decreases dorsal width.

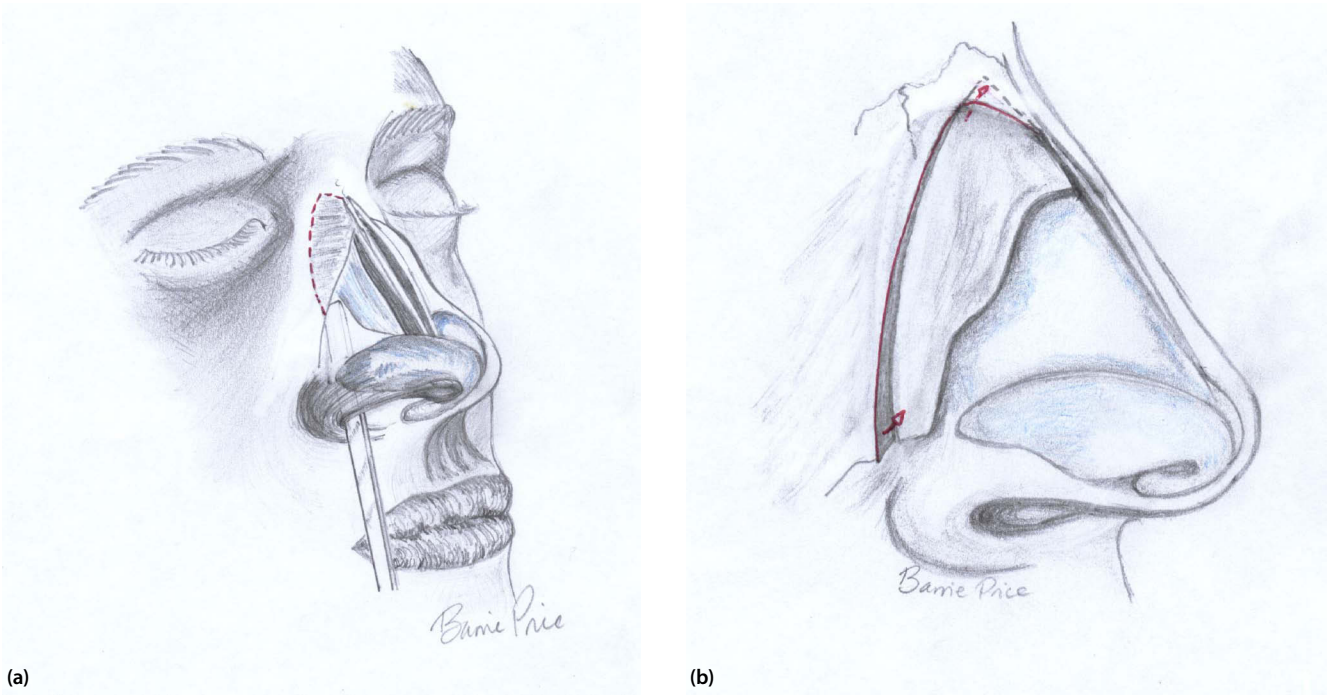
Tardy[16] describes incremental dorsal reduction but starting with retrograde shaving and removal of the intact upper lateral/quadrilateral cartilage hump from the bone–cartilaginous junction at the pyriform aperture to the anterior septal angle. The upper laterals are not released from the septum and therefore this resection will include the horizontal component of these cartilages as well as the dorsal septal quadrilateral cartilage. The bone is then reduced prograde with an osteotome from caudal to cephalic. This hump resection may be performed en bloc. Cartilage and bone are removed as a single unit with the bony and cartilaginous hump attached to each other.

Preservation of the upper lateral cartilages in their horizontal component both between the reduced edges of the bony dorsum and distally, caudal to the bones, maintains structure that can potentially be used to restore or maintain middle-third width and to bridge any gaps between the nasal bones after infracture. The medial edge of the upper lateral cartilages can be folded medially into the nose and sutured to the septum. These autospreader flaps[17] act to maintain mid-third width and are cartilage sparing, being an alternative to spreader grafts. Variations and refinements of these flaps have been described.[18] If the middle third requires width maintenance, there may be insufficient upper lateral to use as a flap. This occurs particularly if a small hump has been removed. In such cases spreader grafts are used. Spreader grafts may also be tailored to requirements better than autospreader flaps if the septum is curved or differential width restoration is necessary.[19] One or the other can be used on either side, depending on anatomical findings (see **Figure 84.1**). The author does not extend spreader grafts all the way to the anterior septal angle as this risks excess caudal mid-third width. There is no horizontal component to the normal upper lateral cartilages in their distal third. If spreader grafts are chosen and they extend to the keystone area, the horizontal component of the upper lateral cartilage in this region must be excised so that it does not sit up over the graft and cause a dorsal irregularity. This can be a technically difficult area to achieve a smooth contour for, particularly between the nasal bones. Preserved upper laterals can be sutured together in the midline after hump resection over spreader grafts.[20] This author also raises a perichondroperiosteal flap from the upper lateral cartilages and nasal bones to close over the dorsum after middle-third reconstruction with or without a contour refining onlay graft deep to the flap. If the middle-third width is good, as may be the case in conservative hump reduction with long nasal bones, spreader grafts or autospreader flaps may not be required. In these cases it is important to suture the upper lateral cartilages back onto the septum to maintain their length, tension and projection.[21] If mid-third vault width is not maintained or reconstructed, dorsal reduction will lead to an inverted V deformity seen in the frontal view. This results from medial and posterior relocation of the upper lateral cartilages and loss of a smooth continuous contour with the bony pyriform aperture.

While dorsal reduction may result in narrowing of the middle, cartilaginous vault, it will also result in widening of the bony vault. Osteotomies may therefore be required to narrow the bony dorsum. They may also be indicated if the bony base width is greater than the intercanthal distance. If middle-vault reconstruction is performed with spreader grafts or autospreader flaps, osteotomies are performed before these techniques are employed. We perform the lateral osteotomies first. These follow a 'low-to-high' path. A stab is performed in the nasal mucosa just superior to the insertion of the inferior turbinate bone onto the maxilla at the pyriform aperture. A 3 mm osteotome is engaged and passes in a gentle superoanterior arc to the level of the medial canthus. This osteotomy can be performed percutaneously. To control the cephalic position at which the lateral bony wall fractures, a 15-degree medial oblique osteotomy is performed from the lateral edge of the open roof to the superior extent of the lateral osteotomy (**Figure 84.3**).[22, 23] A paramedian, medial osteotomy, particularly if in the midline, risks a rocker deformity, either from the medial edge of each nasal bone becoming more projected or the cephalic margin pivoting laterally as the caudal margin is mobilized medially.

If the bony open roof does not extend to the level of the medial canthus, an alternative is to remove a cephalic wedge of bone that will extend the open roof to the level of the medial canthus.[24] A percutaneous, superior transverse osteotomy is then performed laterally from the apex of the open roof to join the cephalic end of the lateral osteotomy. Gentle pressure is applied either side of the dorsum to bring the bones together. Excess pressure at the bony nasal base is avoided to minimize the risk of moving the lateral nasal walls into too vertical a position, creating an unnatural, overly thin nose in the frontal view. Sheen described use of a low-to-high lateral osteotomy only, relying on digital pressure to create a short, superior fracture line along which the lateral wall hinged.[25] We prefer to use this technique only when the bony nasal dorsum is open cephalically to the level of the medial canthi. The technique also assumes that the open roof is wider caudally than cephalically. If this technique is employed for smaller open roofs, we feel it increases the risk of a visible step in the mid lateral nasal wall. In such cases no medial osteotomies will be required and superior, transverse osteotomies are performed to control the position of the superior fracture line as described above.

When the hump is removed, a slightly convex line of nasal bone and cartilage should remain. This allows for the differential thickness of the overlying soft tissues and



(a) (b)

Figure 84.3 **(a)** Endonasal low-to-low lateral and medial oblique osteotomies. **(b)** Movement produced by infracture.

will result in a straight external lateral profile. The author feels this point has been traditionally overemphasized and that any convexity should be slight.

If an open roof requires closing but the nasal base is narrow, infracture carries the risk of producing excess base narrowing. This is of particular concern if the nasal bones are short. Infracture carries the risk of producing excess mid-third narrowing and an inverted V deformity.[5, 26] In these circumstances the dorsum may be better reconstructed with spreader grafts,[5] an onlay spreader graft[27] or a dorsal onlay graft[28] and without osteotomies and infracture. Skoog described modification and replacement of the removed hump for dorsal reconstruction with or without lateral osteotomies.[29] The push-down operation and subsequent modifications have also been described in the management of the convex dorsum to avoid a skeletonized, inverted V deformity consequent upon dorsal reduction.[30]

If a small hump has been removed, an open roof defect may not result. The majority of the hump removed will have been cartilaginous, leaving no significant open bony defect. The upper lateral cartilages may still be contiguous with the quadrilateral cartilage as only the ridges of the bifurcated, 'Y'-shaped cartilaginous dorsum will have been shaved.[31, 32] In such instances, particularly in patients with thick skin and a nose with a narrow base, osteotomies and infracture may not be necessary.

Lastly, the author assesses the dorsum for irregularities with inspection and particularly with palpation using a wet finger. Achieving a smooth contour may require finesse achieved with the use of softened, small cartilage onlay grafts, 'scales' of shaved cartilage, scraped cartilage 'paste' or deep temporalis fascia (see **Figure 84.2**). The author avoids alloplasts.

The septum is quilted with 4/0 or 5/0 polyglactin (Vicryl®) and all incisions are closed with interrupted 6/0 polyglactin (Vicryl®). Great care must be taken with the columella closure to ensure skin-edge alignment and eversion. The author does not insert nasal packing. On induction of general anaesthesia, 8 mg of dexamethasone and a broad-spectrum antibiotic are given intravenously. The nose is taped and an external splint applied which remains for 1 week. Wounds are kept clean postoperatively using 3% hydrogen peroxide, and an antibiotic ointment is applied regularly for 1 week.

OUTCOME ASSESSMENT AND THE FUTURE

While not specifically reporting results of reduction rhinoplasty, several studies demonstrate psychological benefit from cosmetic rhinoplasty.[33–35] The functional sequelae of osteotomy with infracture in reduction rhinoplasty have been objectively studied. No change in nasal resistance using posterior rhinomanometry was detected in a series of 27 patients undergoing open rhinoplasty with osteotomies and infracture. However, patients in this study routinely underwent outfracture with or without submucosal diathermy of the inferior turbinates.[36] Total minimal cross-sectional area and minimal cross-sectional at the piriform aperture, measured with acoustic rhinometry, have been shown to change significantly following reduction rhinoplasty. In this study, 3 patients of 37 complained of postoperative loss of airway patency, which was normal before surgery.[37] No difference was detected between high or low insertion level lateral osteotomy in a 16 cadaver study performed by the same group.[38]

Outcome assessment in facial plastic surgery is a newly developing field looking at results from the patient's perspective. Expanded measures of both quality of life and health perception as well as satisfaction with appearance are studied rather than the surgeon's assessment of technical success.[39, 40] Specific instruments have been proposed for rhinoplasty.[41] International patient-reported outcome measure guidelines and criteria have been developed and from these have arisen patient-related outcome measurement tools that are procedure-specific, such as the FACE-Q.[42] A scale for rhinoplasty will be produced. Psychological screening tools will help us improve patient selection for surgery alongside measuring benefit.[43, 44] Three-dimensional imaging will further help with analysis, planning, communication, management of patient expectation and objective measurement of surgical change.[45]

Technical innovation will continue and will help the surgeon visualize the nasal skeleton better, and more precise techniques for osteotomy[46] and bone sculpting will develop further.

BEST CLINICAL PRACTICE

- ✓ Determine the ideal dorsal line from the ideal nasion and ideal tip-defining point.
- ✓ Use minimally traumatic techniques exploiting natural tissue planes.
- ✓ Fully expose the middle and upper nasal vaults in the midline.
- ✓ Perform dorsal reduction and osteotomies before septoplasty.
- ✓ Avoid aggressive over-resection.
- ✓ Ensure the middle vault is reconstructed.
- ✓ Meticulously assess the dorsum for irregularities after resection and infracture.

KEY POINTS

- Perform thorough pre-operative analysis of nasal deformity.
- Indications for reduction rhinoplasty are excess dorsal convexity relative to ideal height and position of the nasion.
- Aim for a strong, high nasal dorsum with tip projection above the dorsal line.
- Ensure middle vault support to maintain frontal view dorsal aesthetic lines and nasal function.
- Psychological benefit has been demonstrated in observational studies following cosmetic rhinoplasty.

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CHAPTER 85

NASAL RECONSTRUCTION

Ullas Raghavan

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SEARCH STRATEGY

Data in this chapter may be updated by Medline and Medscape searches using the keywords: nasal soft tissue defect, nasal obstruction, nasal skin cancer as specific or individual words that appeared as a keyword, in the title or abstract.

INTRODUCTION

Reconstruction of the nose poses several unique problems. The contours of the nose are variable, with convex and concave surfaces in close contact with each other, and the skin texture and colour is not easy to match. The human eye easily detects the slightest variation in contour or symmetry. Nasal defects can be reconstructed with local, regional, distal or free flaps. The primary aim of reconstruction is to restore the lost function and the secondary aim is to make the reconstructed part as normal in appearance as possible. The aetiology of nasal defects is shown in **Table 85.1.** Essentially, the surgeon confronted with a nasal deformity has to weigh up the alternatives available and select the correct one in order to obtain the best cosmetic and functional result with the minimum donor site morbidity. The selection of method is frequently based on personal experience, known effective procedures or individual bias.[1] Nevertheless, the principles laid out in this chapter and the key points should be of use whatever the choice of technique.

HISTORY

The history of nasal reconstruction dates back more than 3000 years. This operation developed in three phases. The first book on this subject is believed to be by Sushrutha[2] who lived approximately 600 BC. He used flaps from the cheek to reconstruct a lost nose. Later, Indian surgeons used a forehead flap, now universally known as the 'Indian method'.[3] Although this method continued to be used for centuries, it was not developed any further in India.

The next phase of development of nasal reconstruction took place in Italy during the Renaissance. In the mid 15th century, the Branca family in Sicily performed nasal reconstruction, possibly using the Indian method. This was later taken up by Tagliocozzi and published by him in 1597.[4]

TABLE 85.1 Aetiology of nasal defects

Defect type	Defects
Congenital	'Cleft nose', bifid or aplastic nose, proboscis lateralis
Traumatic	Iatrogenic: Septal surgery, scarring from endotracheal or nasogastric tube Thermal, radiation, chemical, mechanical, human bite, avulsion, frost bite
Inflammatory	*Autoimmune:* Wegener's granulomatosis, SLE, sarcoidosis, Sjögren's syndrome *Infection:* Syphilis, yaws, pinta, rhinoscleroma, leprosy, tuberculosis, histoplasmosis, mucormycosis, aspergillosis
Tumour	Basal cell carcinoma, squamous cell carcinoma, malignant melanoma

He used skin from the upper arm to rebuild the nose. Following the death of Tagliacozzi there is no information available to us on nasal reconstruction for two centuries.

After Britain established contact with India in the 18th century, the European surgeons absorbed and developed the 'Indian' operation. The first article that described the Indian method of rebuilding the nose was published in a lay journal called the *Gentleman's Magazine* in 1794.[5] Joseph Constantine Carpue began to perform similar nasal reconstruction after practising on cadavers, and he published his work in 1816.[6] Von Graef in Germany adopted this technique and performed an Indian type of reconstruction in 1816. Warren, a surgeon from Boston, came to Europe to study nasal operations. When he returned to the United States, he performed his first Indian-type nasal reconstruction in 1834.[7] During the 19th century, the Indian technique became widely accepted for rebuilding the nose in North America and even today it remains the basis for most reconstructive procedures.

The idea of rebuilding the nose with a single forehead flap with an inner lining of skin was reported by Natalie in 1842, Johann Friedrich Dieffenbach in 1845 and Ernst Blasius in 1848.[8] The use of composite grafts from the ear for reconstruction of a nasal defect was described by Konig in 1902.[9] In 1943, Gillies reported nasal reconstruction using a composite graft of auricular skin with attached conchal cartilage.[10] He transplanted a free composite auricular graft with epithelium on one side to a forehead flap. After healing took place, the forehead flap with graft was brought down to the nasal defect. Later, extensive work on the use of composite grafts in the head and neck region were reported by Walters.[11] In the 1960s and 1970s, Millard published a series of articles describing the paramedian forehead flap.[12] This helped provide a longer flap so that nasal tip defects could be corrected. More recently, Burget and Menick[13] have refined previous ideas and focused on methods that respect the aesthetic contours of the nose.

ANATOMY

The nose can be divided into upper, middle and lower thirds; the upper third is supported by the nasal bones, the middle third by the upper lateral cartilages and the lower third by the lower lateral cartilages. Contrary to what many believe, the lower lateral cartilages do not extend to the margins of the rim of the nostrils. The thickness and attachment of the skin and subcutaneous tissue to the bones and cartilages vary in different parts of the nose. Over the nasal bones the skin is loosely attached, whereas it is firmly attached to the upper and lower lateral cartilages. The skin over the lower third of the nose can be thick and sebaceous but in some women it can be so fine that the lower lateral cartilages can be seen through it.

AESTHETIC SUBUNITS

Gonzalez-Ulloa et al described the facial aesthetic units.[14] Aesthetic subunits are segments of contour broken by a change in undulation, skin quality or shadow. Different facial regions have their own colours, textures, mobility and contour. Every region is distinguished from other regions by its pattern of hair growth, quality and skin texture.[15] Scar placements along the border of the subunits can minimize visible alterations in contour and texture. The subunits comprise five convex and four concave units (**Figure 85.1**). They are the tip, dorsum, paired sidewalls, paired ala-nostril sills, soft triangles and columella.[16] In order to obtain an optimum cosmetic result, Burget and Menick[16] have advocated that the whole of the subunit is replaced. Defects that involve more than half a subunit should be repaired after removing the normal tissue in that subunit so that the whole subunit can be replaced.[16] Nasal defects may extend to

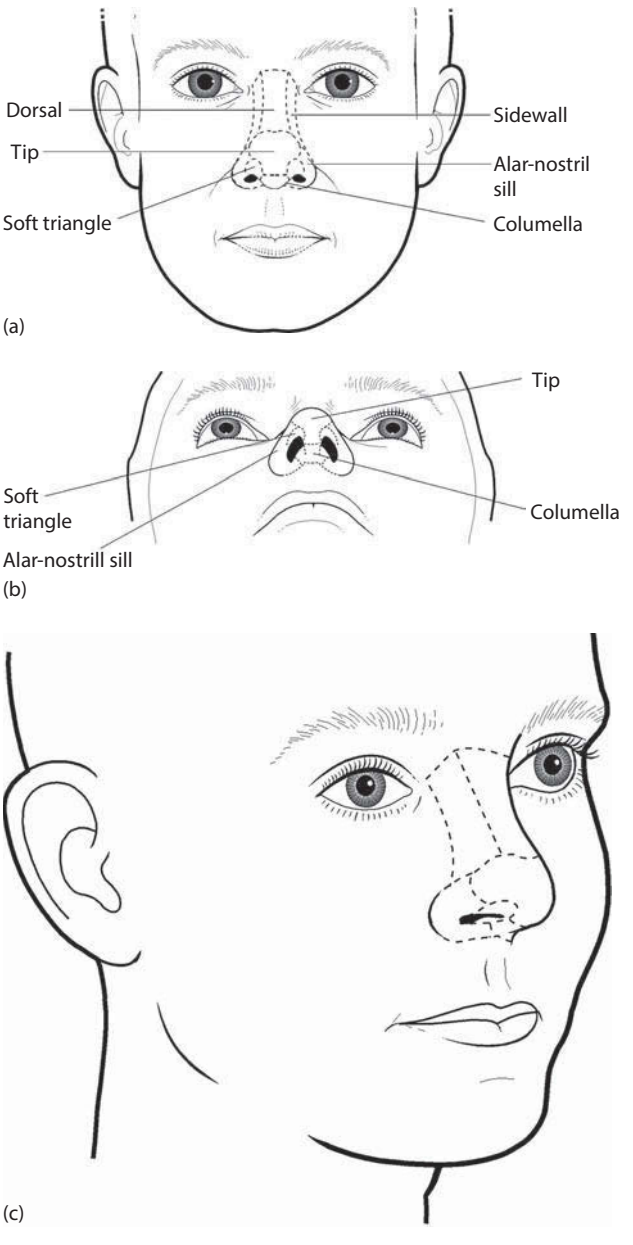


Figure 85.1 The aesthetic units of the nose.

adjacent facial units. The reconstruction of these facial units should ideally be carried out with a separate flap to maintain the segmental quality of the face.[16]

PRINCIPLES OF NASAL RECONSTRUCTION

After reconstruction, the nose must function and be aesthetically pleasing. The nasal valve, the inner lining of the nose and its supporting cartilages determine whether it works. Cosmesis depends on the cartilage and bony scaffolding, the quality of the skin, symmetry and the aesthetic compartments. Burget and Menick[13] have illustrated the primary principles in nasal reconstruction in an excellent text on this topic that is essential reading for any surgeon undertaking this work. They place particular emphasis on matching the contour of the unaffected side in unilateral defects, and respecting and reproducing aesthetic units wherever possible. They caution against using a forehead flap with any tissue excess as it will contract and 'bunch up' through contraction.[16] The fundamental principle of nasal reconstruction is to recreate the missing structures as closely as possible. Other principles include: avoid tension; replace whole aesthetic segment (where >50% loss); try to replace the exact amount of tissue, excess flap or graft may 'bunch up'; approximate vascularized tissue to any graft to avoid dead space.

During reconstruction of the nose, aesthetic segments must be respected as far as possible and the result is often better when the whole aesthetic segment, rather than part of it, is replaced. When the defect crosses aesthetic boundaries, more extensive reconstruction may be required. This is common in the nose and medial canthal regions, especially following Mohs' micrographic surgery for squamous cell carcinoma or morphoeiform basal cell carcinoma. A full-thickness defect of the nose also needs a lining, a scaffold and an external layer of skin of the same quality in terms of thickness, degree of sebaceous tissue and, if possible, colour, as the defect that is being replaced. Any cartilage that is removed needs to be replaced to avoid distortion and maintain symmetry. Another principle is to replace like with like so that the loss of an upper lateral cartilage should be replaced with cartilage of the same shape and thickness, if possible. In addition to this rule, a strut of cartilage should support the margin of the nostril where no cartilage normally exists, otherwise notching of the margins occurs. Extensive nasal defects that result from nasal malignancy require a combination of flaps and grafts as reconstruction will require an inner and outer layer, as well as supporting cartilage.

It is worth noting that, without the support of any septum, nasal reconstruction of the nose using any type of graft or flap is difficult. An osseointegrated replacement or prosthesis is another alternative. One possible technique to overcome this problem is the use of free bone and cartilage grafts sandwiched between a pericranial and paramedian forehead flap.[17]

PHYSIOLOGY

Factors influencing nasal reconstruction include:

- the aetiology of the defect and prognosis
- whether the patient has had previous radiotherapy, smokes, suffers from diabetes mellitus or has scarring from previous surgery
- the patient's nutritional status
- the patient's aesthetic needs and psychology.

Reconstruction is carried out using flaps or grafts. While flaps derive nutrition from their own blood supply, free grafts do not have a vascular pedicle. Grafts undergo three distinct, but overlapping, stages of healing.[18]

- **Stage one** is that of plasma imbibition. This stage begins at the time of graft placement and continues for the first 24–48 hours. Fluid is absorbed into the graft by capillary action, which draws the plasma into the graft itself. During this period, a fibrin deposit is being laid down between the graft and the recipient bed, which helps hold the graft in place. This process can be easily disturbed with the accumulation of clot or serum beneath the wound, separating the graft surface from the recipient bed.
- **Stage two** of graft healing begins approximately 24 hours after placement of the graft; the vascular components from the recipient bed start to meet with vessels randomly in the graft. At this point, circulation is beginning within the graft.
- **Stage three** includes vascular bud growth into the graft developing a vascular network. If anastamosis between the bed and graft is successful, true circulation begins within the graft and continued healing begins.

Direct interface between the graft and the recipient bed is important and this should be maintained during the first week.[19] Loose quilting may be necessary. Quilting should not be tight as post-operative swelling can cause excessive tension and lead to pressure necrosis.

The size of composite graft is important as blood vessels only develop from the edges. The vascularization of a composite graft is somewhat more tenuous and is dependent on limited surface contact along the edge of the graft and reducing any movement between the graft and its bed to a minimum.[10, 20] In larger grafts, survival depends on the rate of vascularization versus the rate of any destructive process.[20] The usual recommendation is that the centre of a free graft should not be more than 0.5 cm from the source of its blood supply. However, Converse[21] used an auricular composite graft up to 2.5 cm in diameter. The failure of a graft to survive in its new recipient area is more than a great disappointment to surgeon and patient, for the resorption of a necrosed cartilage transplant leaves a mass of scar tissue which renders further repair of the deformity much more difficult.[22]

TECHNIQUES FOR NASAL RECONSTRUCTION

Table 85.2 summarizes the techniques available for nasal reconstruction.

TABLE 85.2 Reconstruction of nasal defects

Area	Technique	Type
Skin and subcutaneous tissue	Primary closure	
	Secondary intention healing	
	Skin graft	Split thickness Full thickness, e.g. preauricular
	Local flaps	Advancement flap, e.g. cheek flap Rotation flap, e.g. dorsal nasal flap Transposition flap, e.g. bilobed flap, melolabial flap, nasolabial flap
	Regional flap	Pedicled, e.g. paramedian forehead flap Microvascular, e.g. dorsalis pedis free flap
Skeletal structure	Cartilage	Septal cartilage Conchal cartilage Rib cartilage
	Bone	Iliac crest Skull
Inner lining	Skin	Local flap Composite conchal graft 'Visa' of nasal vestibular skin
	Mucosa	Local flap Pedicled septal mucosal flap Composite conchal

Excision and primary closure

Small nasal lesions can often be excised and repaired by primary closure. Whole-thickness defects greater than 0.5 cm diameter repaired by this technique will often result in some asymmetry. Loss of skin and subcutaneous tissue, if minimal, can be closed after undermining either side down to the cartilaginous or bony skeleton. The advantages of this procedure are that it is a simple technique and single-stage.

Excision and healing by secondary intention

Healing by secondary intention is simple, does not require further surgery or hospitalization and it avoids donor site scarring and pain.[23] It also allows early detection of recurrence of cancer. Wounds allowed to heal by secondary intention do not necessarily give a bad scar.[24] In certain clinical situations, the scar from secondary healing will be better than a scar from a standard surgical repair. The variables to consider when deciding to opt for healing by secondary intention are the position, depth and size of the wound, skin colouration and patient age.[25] The most favourable sites are the concave surfaces of the nose, ear, eye and temple (NEET areas).[26] The disadvantages of this mode of healing are inconvenience due to a protracted healing time, infection, hypertrophic granulation tissue and scarring, hypopigmentation and distortion of adjacent structures through cicatrization.

Skin graft

Wounds that cannot be closed primarily or are not suitable for healing by secondary intention require repair with either a skin flap or a skin graft. An advantage of skin grafts is that they are the simplest and most predictable method of resurfacing a nasal defect not amenable to primary closure. Their disadvantage is a suboptimal cosmetic result due to contracture, poor colour match, a tendency to contract around the edges and donor site morbidity.[27] Split-thickness skin grafts contract more than full-thickness skin grafts post-operatively and their colour, texture and thickness will not readily match the surrounding skin. The full-thickness skin graft (Wolfe graft) contains most of the structures of the skin and is cosmetically superior to split-thickness grafts. The full-thickness skin graft is limited by its donor site availability and has an unpredictable 'take' over 2.5 cm. This can be used to resurface a defect of the upper two-thirds of the nose. The structural support should be intact. This graft often gives a poor result when used to replace the skin of the lower third of the nose as the smooth graft will contrast with the thick and sebaceous skin that is common in this area. For a full-thickness graft to take, the underlying periosteum and perichondrium should be healthy and vascular and the graft must remain immobile for vascularity to develop. The preauricular area is an ideal donor site as the graft often matches the skin of the upper two-thirds of the nose in colour, thickness and texture.

Local flaps

Local or adjacent skin flaps have many advantages. They have their own blood supply and, when designed well, the healing rate is high and the post-operative contraction is minimal. Local flaps are best for reconstructing the convex subunits of the nose. Depending on the vascularity, local flaps can be divided into random or axial. There are limits to the length and size of random local flaps that are based

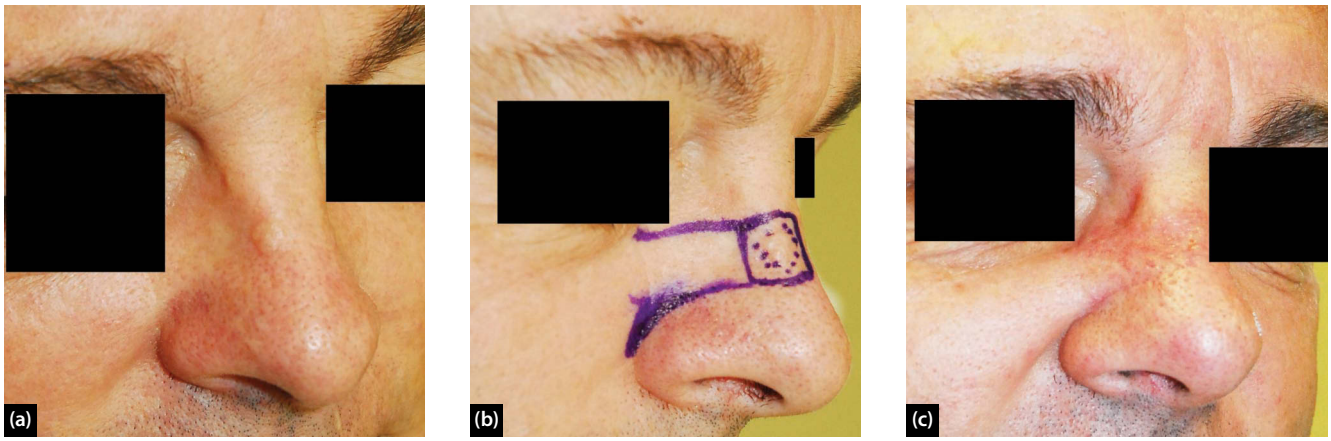


Figure 85.2 Advancement flap. **(a)** Nodular BCC of the nasal dorsum. **(b)** Excision margin and advancement flap marked. **(c)** Post-operative appearance after 6 months.

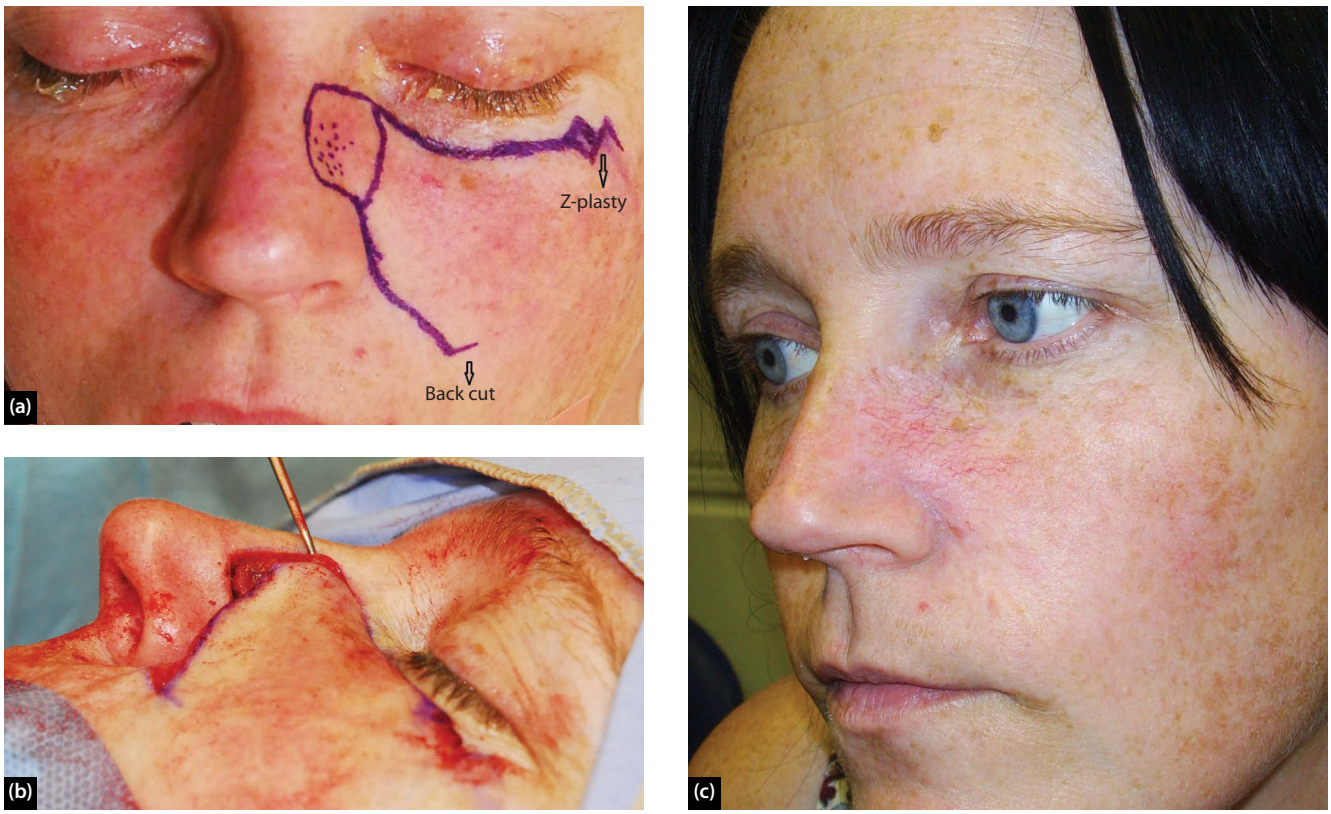


Figure 85.3 Cheek advancement flap. **(a)** Lentigo maligna of the nasal dorsum with cheek advancement flap marked with Z-plasty and back cut to lengthen the flap. **(b)** Flap raised and positioned. **(c)** Post-operative appearance after 1 year.

on random blood supply[28] but axial flaps based on named blood vessels can be larger. It is best to undermine below the subcutaneous musculoaponeurotic system (SMAS) in order to maximize the blood supply. Wide undermining is needed to reduce tension and increase the mobility of the skin and subcutaneous tissue. Based on their movement, local flaps are subdivided into advancement flaps, rotation flaps, transposition flaps and interpolation flaps.

ADVANCEMENT FLAP

Advancement flaps are the simplest of local flaps, being created when the tissue is undermined and advanced in a straight line in the same axis as the defect. An example of an advancement flap is the rectangular flap (**Figure 85.2**). Burrows triangles are excised to avoid 'dog ears', the cheek advancement flap and the V–Y advancement flap.[29] If the defect is large, two rectangular advancement flaps can be used to close the defect in an 'H' fashion. The reach of the advancement flap can be increased by using a 'Z'-plasty and/or a back cut (**Figure 85.3**). In a V–Y flap the flap is designed to be about twice the size of the defect (**Figure 85.4**). A bipedicled advancement flap can be used for closing a defect of the nasal dorsum (**Figure 85.5**).

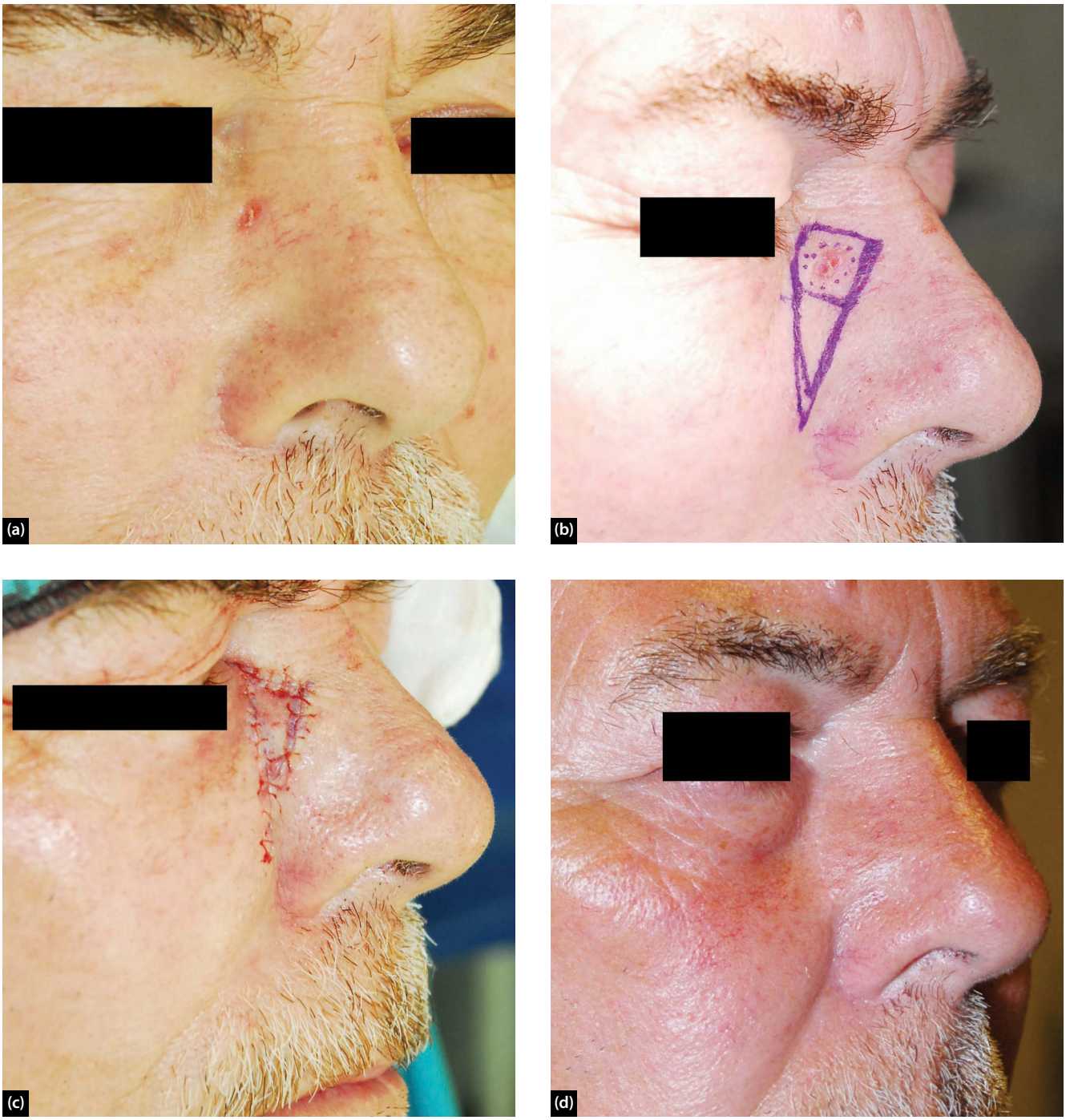


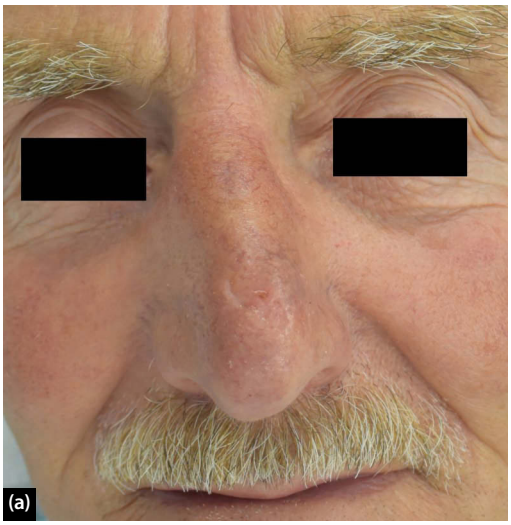
Figure 85.4 V-Y advancement flap. **(a)** Infiltrative BCC of the nasal side wall. **(b)** Margins and flap designed. **(c)** Flap sutured to the defect. **(d)** Post-operative appearance after 1 year.

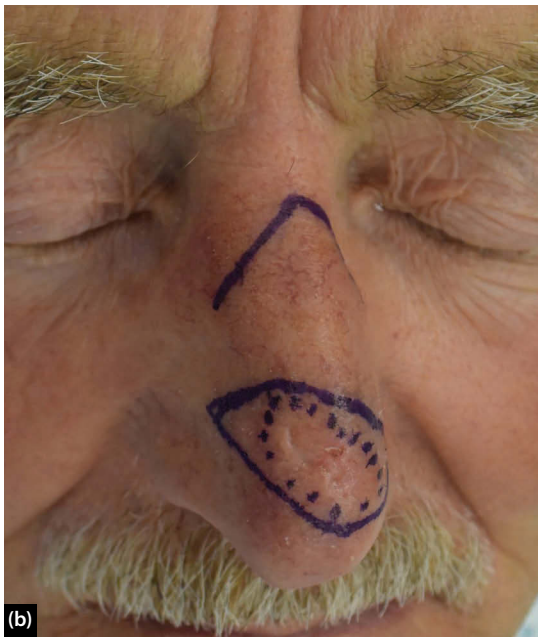
ROTATION/PIVOT FLAP

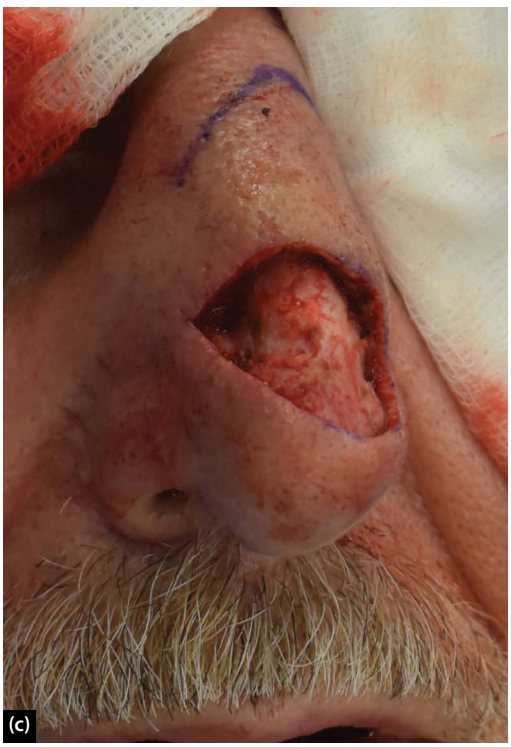
A pivot flap is one whose axis rotates around a pivot to close the defect. As the degree of rotation increases, the effective length of the flap decreases. The entire flap and the surrounding skin need to be undermined in all directions. Failure to do this results in excessive tension during closure and buckling and will possibly compromise vascularity.[29] A bilobed flap is an example of a pivot flap. This is ideal for small defects (<1.5 cm) on the lateral side of the nose where local skin of the same thickness and colour can be used to fill a defect. If these flaps rotate skin through an arc of more than 110 degrees in the relatively inflexible thick skin of this region, it produces a prominent dog ear.

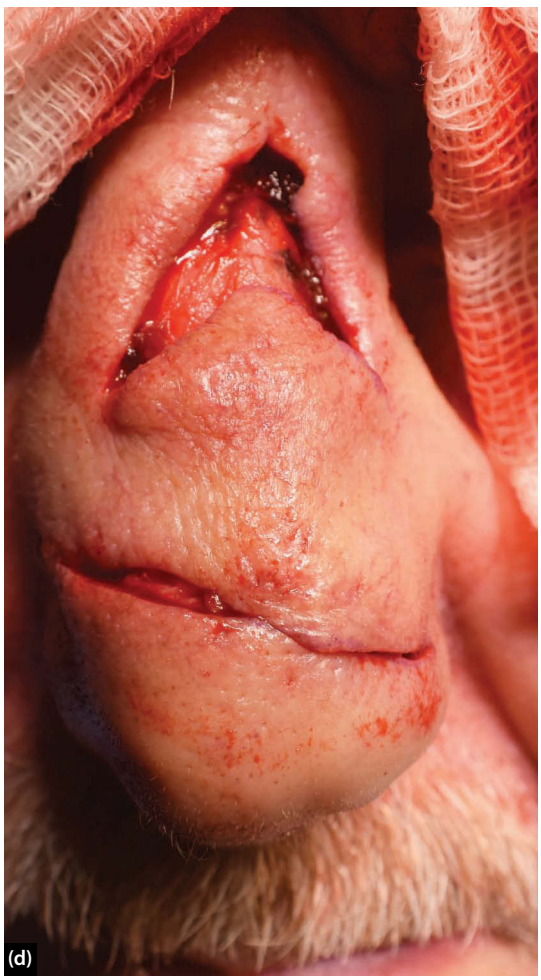
TRANSPOSITION FLAP

Transposition flaps are adjacent to the defect and do not have to cross an intact bridge of skin. They allow movement in more than one plane and examples include the 'note flap' and the rhomboid transposition flap.[18] A bilateral rhomboid flap has been described to reconstruct a supratip defect.[30]









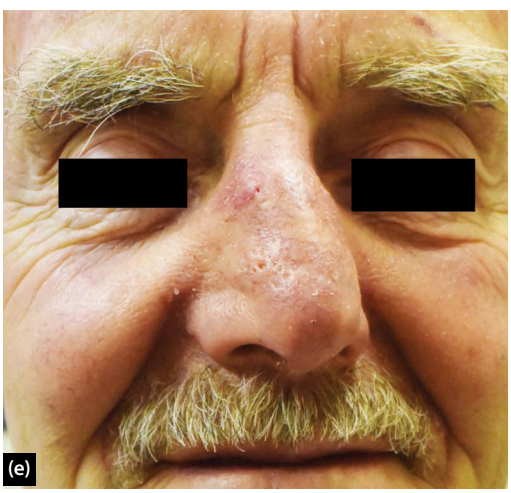


Figure 85.5 Bipedicle flap. **(a)** Nodular BCC of the nasal dorsum. **(b)** Margins of excision and flap marked. **(c)** After excision of BCC. **(d)** Bipedicled flap raised. **(e)** Post-operative appearance after 1 year.

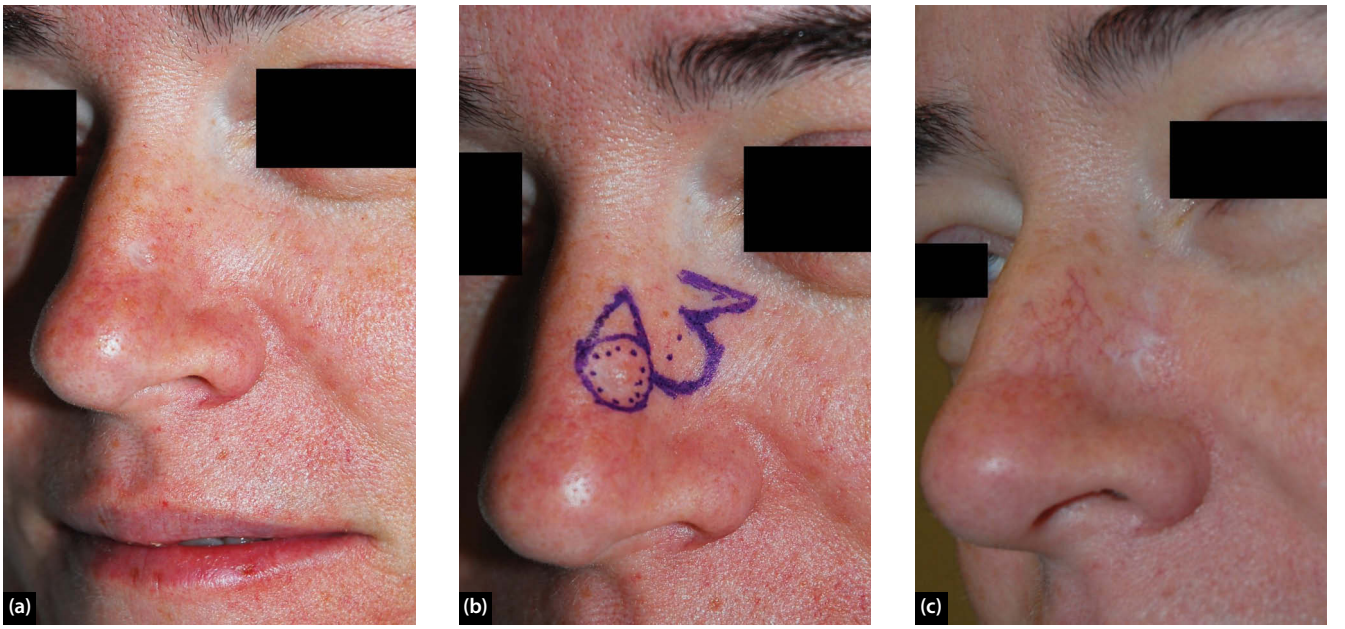


Figure 85.6 Bilobe flap. (a) Nodular BCC of the nasal side wall. **(b)** Excision margin and bilobe flap designed. Shaded area removed to avoid 'dog ear'. Flaps move as shown by the arrows. **(c)** Post-operative appearance after 1 year.

INTERPOLATION FLAP

Interpolation flaps are not adjacent to the defect and they cross a bridge of intact skin to reach the defect. They will require a second stage to cut the pedicle once the flap has developed sufficient vascularity at the recipient site. Paramedian and nasolabial flaps are examples.

Bilobed flap (Zitelli's)

This is the flap of choice for defects of the lower third of nose 0.5–1.5 cm in diameter (**Figure 85.6**). There are five rules for the flap design to avoid problems of contour and vascularity.[31]

- The bilobed flap is used for defects up to 1.5 cm in diameter.
- Each lobe should not rotate more than 50 degrees.
- A piece of skin is excised between the defect and pivotal point of the flap before rotation to avoid a dog ear. The pivotal point is located away from the margin of the defect at a distance equal to the radius of the defect. It is never placed close to the medial canthus or alar margin.
- Lift the flap just above the level of the periosteum and perichondrium in order to preserve its blood supply and minimize scarring.
- The diameter of the first lobe is equal to the defect and the width of the second lobe is less than the first but large enough to close the donor defect comfortably.

Dorsal nasal flap

A dorsal nasal flap (**Figure 85.7**) can be used to cover a defect of the lower third of the nose but is not the ideal choice. The skin and soft tissue are elevated off the periosteum and perichondrium over the dorsum and side wall of the nose up to the glabella. This flap is slid down to cover the defect. The advantages are that the skin is brought from an area of excess, the glabella, to the lower third of the nose and the defect is covered by tissue similar to the lost one. However, it has three aesthetic disadvantages:

- The thick and pitted skin of the glabella slides downwards and may form an epicanthal fold.
- The flap does not coincide with the subunit excision lines.
- It forms a large dog ear that may not be corrected completely.[31]

Glabellar rotation flap

A glabellar rotation flap (**Figure 85.8**) is useful for defects of the upper third of nose and medial canthus. Excess skin from glabellar region is rotated down to cover the defect. Disadvantages are the same as for the dorsal nasal flap.

Nasolabial flap

A nasolabial flap (**Figure 85.9**) is suitable to correct the skin loss of the alar subunit. It can be used as the outer lining layer when a full-thickness defect of the alar subunit is being corrected. The flap can be based inferiorly or superiorly, and the pedicle divided at a second procedure. Alternatively, an island flap can be rotated into position.[32, 33] The perforating branches of facial and angular arteries supply this flap and an island flap can be rotated 180 degrees to allow primary closure. In order to obtain a groove around the alar margin, the nasolabial and cheek skin can be advanced a few millimetres more than might seem necessary and the rim left unsutured so that,

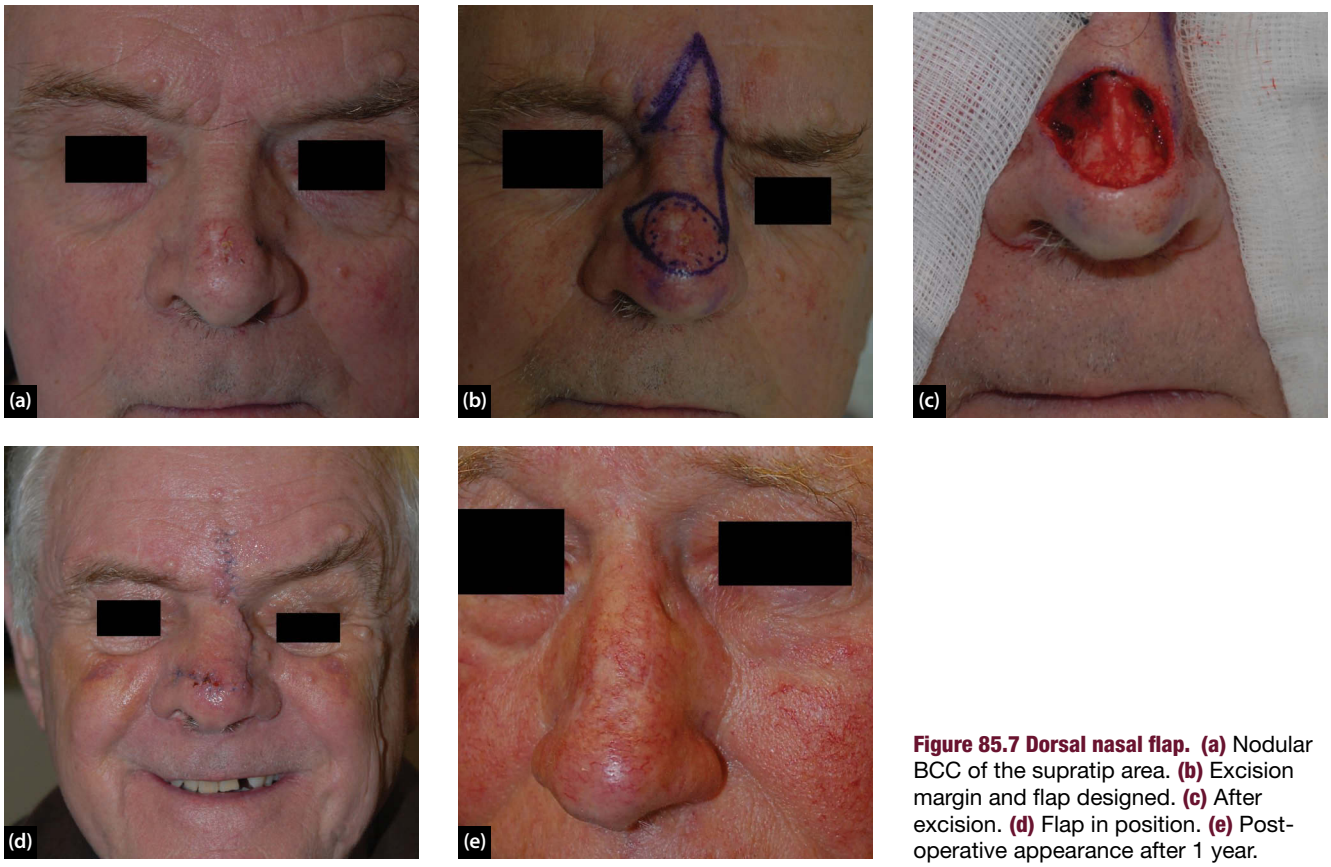


Figure 85.7 Dorsal nasal flap. **(a)** Nodular BCC of the supratip area. **(b)** Excision margin and flap designed. **(c)** After excision. **(d)** Flap in position. **(e)** Post-operative appearance after 1 year.

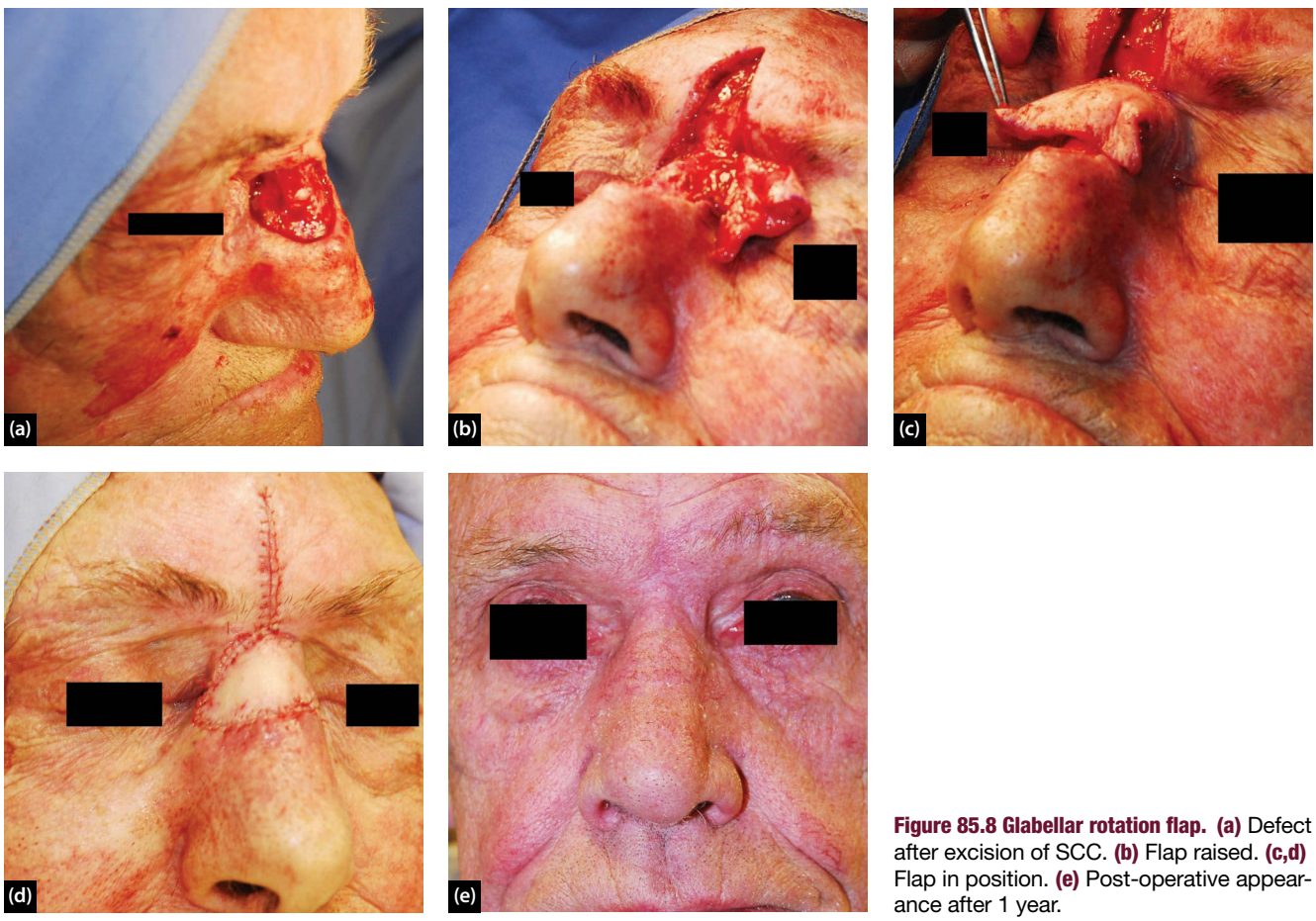


Figure 85.8 Glabellar rotation flap. **(a)** Defect after excision of SCC. **(b)** Flap raised. **(c,d)** Flap in position. **(e)** Post-operative appearance after 1 year.

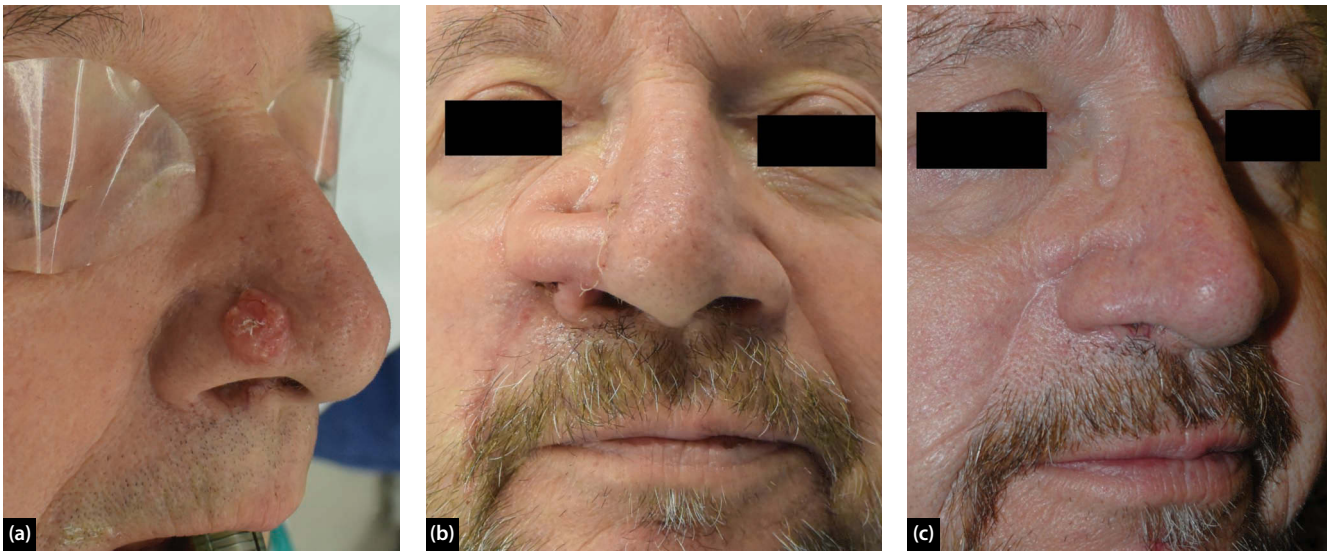


Figure 85.9 Nasolabial flap. **(a)** Nodular BCC of the ala. **(b)** Nasolabial flap in position. **(c)** Post-operative appearance after 1 year.

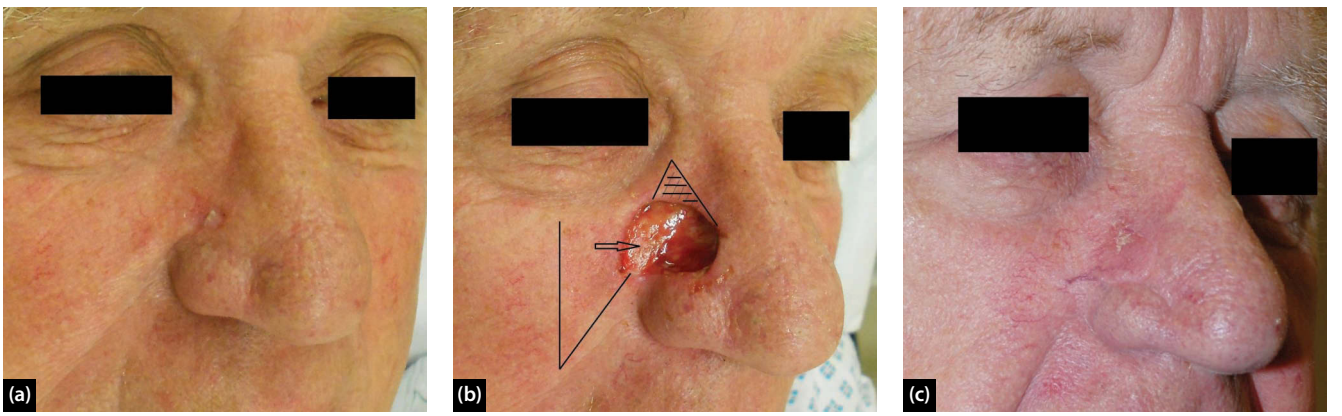


Figure 85.10 Note flap. **(a)** Infiltrative BCC of the nasal side wall. **(b)** Flap designed. The arrow shows the direction of movement of the flap. The shaded area is to be removed to avoid a 'dog ear'. **(c)** Post-operative appearance after 6 months.

when healing takes place, the reconstructed ala contracts a little and rolls up to form a more natural edge.[34]

Note flap

The note flap (**Figure 85.10**) and adjoining defect appear similar to a musical note and hence the name. It is essentially a superiorly based nasolabial flap. A dog ear is removed and the flap moved to cover the defect. A second stage is not required.

Septal flaps

An anterior septal mucosal flap based on the septal branch of the superior labial artery, or alternatively a posterior flap based on the septal branch of the sphenopalatine artery, can provide an internal lining.[16] A septal flap produces a well-vascularized lining and, while it tends to crust for several weeks, it will eventually provide a normal lining. Squamous epithelium will tend to crust for many months when it is used to line the nose. One of the main limitations about using a septal flap is that, if both nasal vestibules need an internal lining, then a septal perforation will almost certainly be produced. Most septal flaps cause nasal obstruction as they fold over and this requires a secondary procedure. It is important to raise these flaps under the mucoperichondrium to give them strength.

Regional and distant pedicled flaps

When there are larger or more complicated defects, including a full-thickness tissue loss, regional flaps may be required. Complications can include: graft necrosis (rare in paramedian forehead flap); intranasal crusting; donor site morbidity; 'bunching up' due to contracture of excessive tissue; stenosis and nasal obstruction.

If pedicled regional flaps are not available, distant pedicled flaps can be used. However, distant pedicled flaps, like the pectoralis major myocutaneous flap and trapezius island paddle flap, do not provide a good colour or texture match for the nasal skin and are very bulky. Free flaps described for use in total nasal reconstruction are the radial forearm free flap, the dorsalis pedis free flap and the retroauricular free flap. The radial forearm free

flap is bulky, the dorsalis pedis free flap is thin, but it causes significant donor site morbidity and the retroauricular free flap has very small vessels and therefore has a precarious vascular anastamosis, limiting its application.

Large or complex defects with a full-thickness tissue defect require regional flaps in conjunction with free or local flaps and grafts. Free flaps have been described for use in total nasal reconstruction but they are bulky as the underlying fat is thick and it is difficult to thin it evenly, even after several stages.[35, 36] A pericranial flap has been described to provide an internal lining for total nasal reconstruction.[17]

The midline and paramedian forehead flaps are the pedicled flaps that are of most use in nasal reconstruction.

Midline forehead flap

For reconstruction of large defects of the nose above the columella, the midline forehead flap can be used, but extension onto the columella is limited. It can be used for subunit repair, heminasal reconstruction or total nasal reconstruction.[37] The midline forehead flap is based on the supratrochlear arteries[38] and consists of skin, subcutaneous tissue and frontalis muscle. A width of up to 4 cm has been described.[37] Recently, a midline forehead flap based on central artery has also been described.[39]

The advantages of this flap are the excellent colour and texture match with the skin of the nose, reliability and low morbidity, and the donor site deformity is low. The disadvantage is that the 180-degree twist in its base means that it has to extend to hair-bearing skin if it is to stretch to the columella without kinking its base. It is also unsightly until a subsequent procedure is carried out to divide the flap.[37]

Paramedian forehead flap

The paramedian forehead flap (**Figure 85.11**) is an improved modification of the midline forehead flap and is the best alternative in dealing with major nasal defects.[40, 41] The technique is very similar to that of the midline forehead flap except that the flap is positioned to one side of the midline based on the ipsilateral supratrochlear artery.

This flap is not only robust but the donor site often heals well, even when it is not possible to close its upper part and this is left to heal by secondary intention. One of the main problems of the flap is its thickness, particularly if it is used to reconstruct the alar margin. It is possible to thin this skin down up to 1.5 cm from its distal rim unless there are adverse factors affecting its vascular bed. A single-stage paramedian flap has also been described.[42]

Multiple flaps in large defects

When the defect is large, the use of multiple local flaps (**Figure 85.12**) can be considered for reconstruction if the patient is not keen on using larger flaps such as paramedian flap or cheek advancement flap. In such cases it may be advisable to use slightly larger flaps to compensate for the possible cicatrization at the junction of the flaps.[43]

Free cartilage grafts

Cartilage from the septum, conchal bowl or rib provides a useful scaffold and it is rare for it to resorb unless it is morselized or becomes infected. The scaffolding should be provided at the same time as the reconstruction. Delay in providing the support leads to scarring and contraction of the flap, causing difficulty in placing the scaffold as a second-stage procedure.[44] Burget and Menick have advocated placing the cartilage between the frontalis muscle and the skin of a forehead flap before any contraction of the flap has occurred,[45] but it can only be placed distally and this may compromise the distal vasculature. When alar subunits are reconstructed, the margin must be supported with a cartilage graft to avoid contracture. These grafts are kept between the inner and external lining to provide adequate blood supply. Even when the defect does not involve the alar margin, the cartilage-free graft has an important role in providing support if the lower lateral cartilage, upper lateral cartilage or quadrangular cartilage is lost.

Composite cartilage grafts

The free composite graft (**Figure 85.13**) consists of skin and greater or lesser amounts of attached subcutaneous tissue. Konig[9] first described the use of a composite cartilage graft from the ear. In his paper published in 1943, Sir Harold Gillies described the use of the composite graft to provide the inner lining of forehead flap used for nasal reconstruction.[10] Limberg,[46] Brown et al[47] and Dupertuis[48] reported the use of a free sandwich graft from the auricle for nasal reconstruction. The free auricular composite graft has been advocated for the repair of minor defects of the lower part of the nose for the following reasons.[48]

- The skin of the ear is similar in colour to the skin of the nose.
- The ear contains cartilage that gives good support with a choice of contours to match those of the ala.
- The auricular graft has only a slight tendency to contract after surgery.
- This method is economical because the length of hospitalization is much shorter.
- The secondary defect of the ear is inconspicuous and can easily be repaired.

Composite grafts up to 2 cm in diameter can survive free transplantation where the vascular bed has not been compromised by smoking, radiotherapy, scar tissue from previous trauma or surgery, diabetes or severe atherosclerosis.

The shape of the auricular composite grafts makes them suitable for use in nasal surgery.[49] These grafts have been used to correct small defects of the alar margins, especially those taken from the antitragal margin. The disadvantages noticed with the auricular composite graft are that, while its contour can often match that of the alar rim, it can rarely replace a whole aesthetic unit

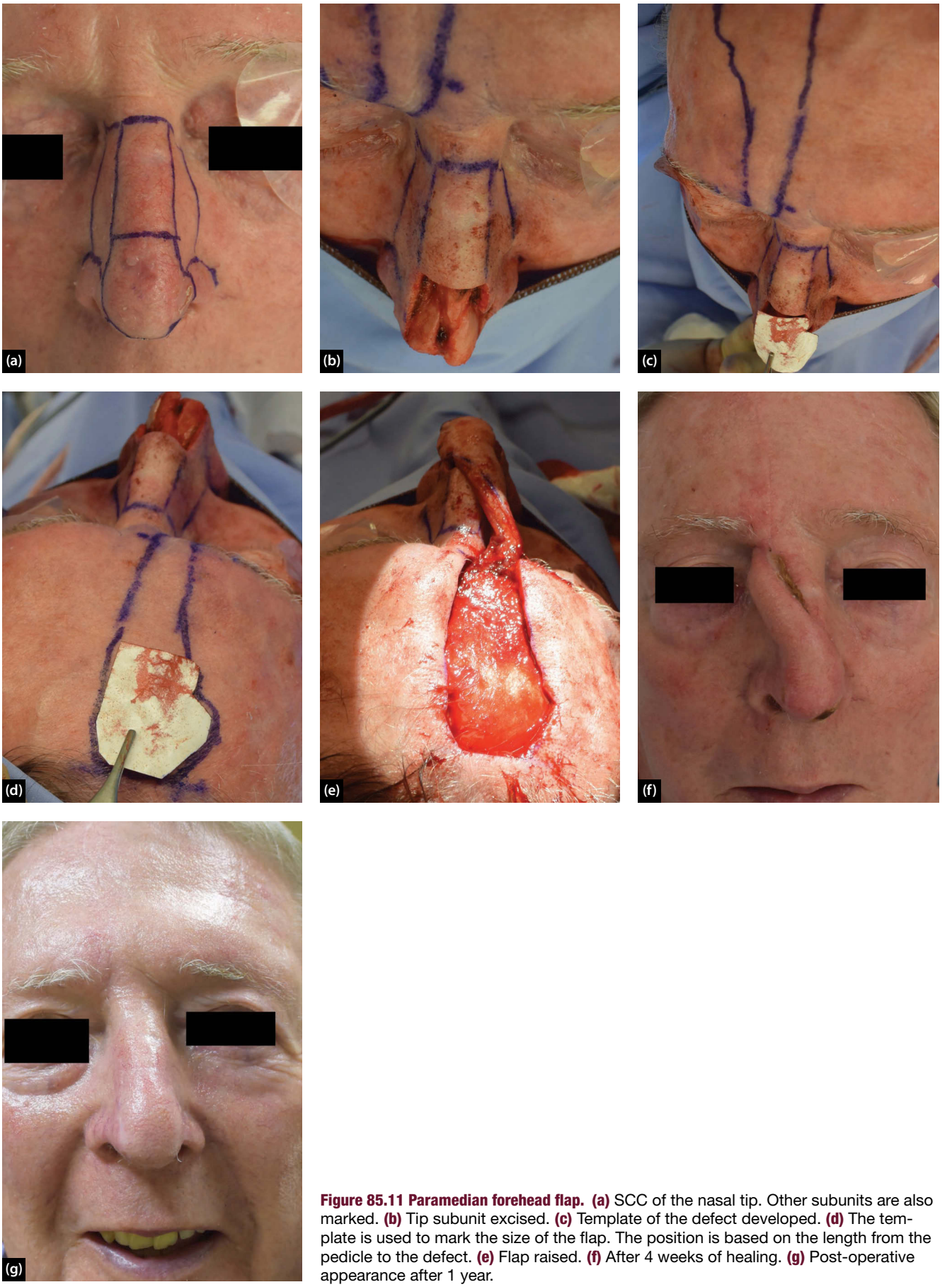


Figure 85.11 Paramedian forehead flap. **(a)** SCC of the nasal tip. Other subunits are also marked. **(b)** Tip subunit excised. **(c)** Template of the defect developed. **(d)** The template is used to mark the size of the flap. The position is based on the length from the pedicle to the defect. **(e)** Flap raised. **(f)** After 4 weeks of healing. **(g)** Post-operative appearance after 1 year.

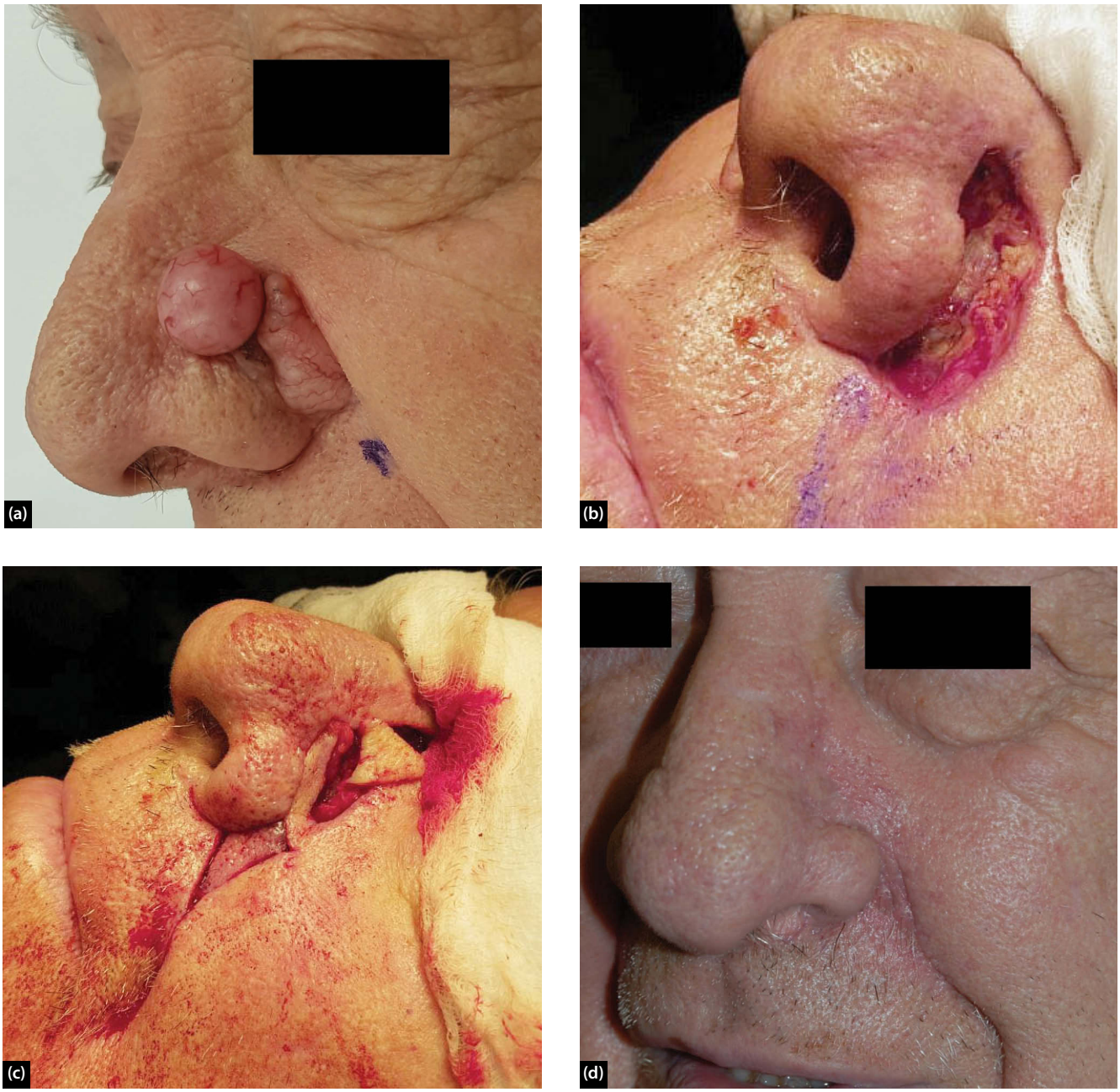


Figure 85.12 Multiple flaps for a large defect. **(a)** Nodular BCC of the alar grove, ala, side wall and adjoining cheek. **(b)** Defect after excision. **(c)** Three flaps raised: two V–Y advancement flaps and a small note flap between them. **(d)** Post-operative appearance after 6 months.

and its skin quality is often different once it has bedded in and fibroblasts have led to some contracture.[50] The auricular composite graft from the conchal bowl can be used for lining the inner surface of the paramedian forehead flap and to provide skeletal support to the reconstructed area.[41] The defect can be filled using a pedicled postauricular island flap.[41] The benefits of a conchal cartilage graft to provide the internal lining and support for a paramedian forehead flap when both nasal vestibules need reconstructing are that it avoids a septal perforation[51] and nasal obstruction and there is little donor site morbidity. The morbidity of the donor region is small.

CONCLUSION

Various techniques are described for reconstructing defects of the nose. The surgeon chooses the technique depending on his or her preference and the nasal defect that requires correction. Whatever technique is used, it is essential to reconstruct all three layers of the nose. Whole aesthetic subunits must be reconstructed for a better aesthetic result if more than half of the subunit has been lost. Although different grafts and flaps have been described, in our opinion, the paramedian forehead flap (with composite conchal graft, if required) is robust and consistently gives good results in major nasal reconstruction.

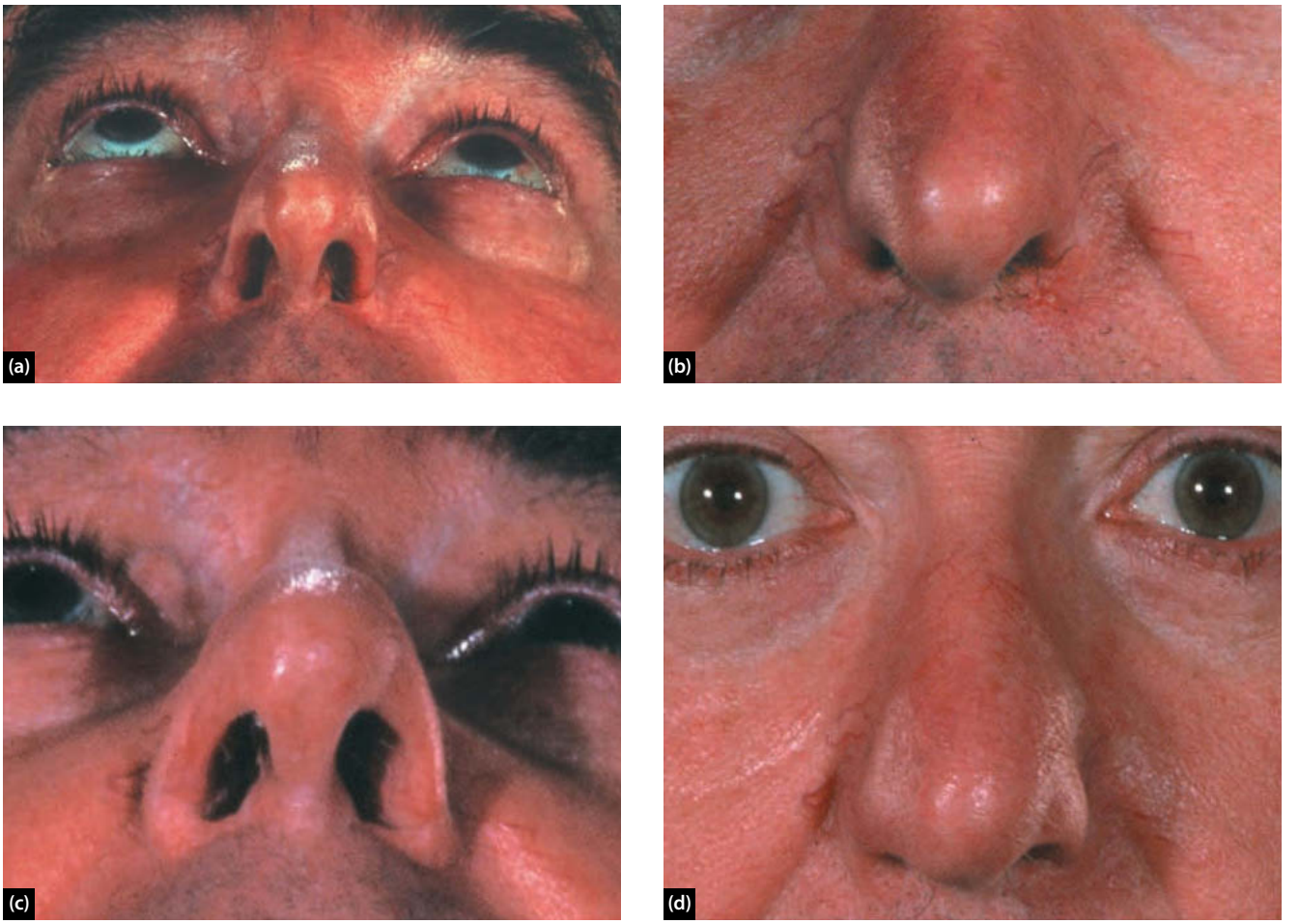


Figure 85.13 Composite cartilage grafts. (a,b) Bilateral vestibular stenosis and notching of the alar margins secondary to pressure from the nasogastric tubes. **(c,d)** Post-operative view after inlay of conchal composite grafts.

BEST CLINICAL PRACTICE

- ✓ Reconstruction should only be undertaken when the surgeon is sure that the tumour has been removed.
- ✓ Mohs' micrographic surgery should be used for morphoeiform basal cell carcinoma or squamous cell carcinoma whose margins are unpredictable. If Mohs' is not available, then it is best to wait for the histological result from paraffin sections and dress the wound in the meantime.
- ✓ The slightest variation in contour or symmetry of the nose is readily seen and the aim should be to obtain as much symmetry as possible.
- ✓ The concept of replacing the whole of an aesthetic segment (a tissue plane with the same thickness, colour and contour of skin) if more than 50% of the segment has been lost is important in obtaining a good cosmetic result.
- ✓ Reconstruction requires an inner lining, scaffolding and an external layer otherwise the tissue will contract, roll up and become thick, firm and featureless.
- ✓ Incisions should be made at the junction of aesthetic segments in order to disguise them.
- ✓ If a defect requires three or more flaps to reconstruct adjoining aesthetic units, there can be unpredicted cicatrization at their junction. This particularly applies to the alar base and in these circumstances we recommended replacing the nasal defect with more tissue in the paramedian forehead flap than when the units of the nose are being reconstructed on their own.
- ✓ It is important for an individual's self-esteem and psychological well-being that they undergo counselling before embarking on nasal reconstruction.

FUTURE RESEARCH

- Many techniques have been described to reconstruct the nose and their success rate in both aesthetic and functional terms is difficult to quantify. The presence of numerous techniques means no one technique is good for all defects of the nose.
- A minority of authors have questioned the principle of resecting the remainder of an aesthetic segment if more than 50% has been lost[52] but these claims have not been supported by photographic evidence equal to that of the proponents of this principle. There are no good techniques available to reconstruct the nose if the septal support is lacking.
- Randomized control trials are unlikely to take place given the relative rarity of these conditions and the number of variables that would need to be controlled for. Nevertheless, the techniques described have stood the test of time and give good results when the principles outlined in this section are followed. These are not procedures that should be 'tried' by the occasional or inexperienced surgeon as a poor outcome makes it far more difficult to achieve a good result if revision surgery is needed.

KEY POINTS

- The concept of an aesthetic segment, a tissue plane with the same skin thickness and contour, is central to obtaining a good result.
- Try to keep the scars parallel to relaxed skin tension lines and at the junction of aesthetic subunits to make them less noticeable.
- Usually whole aesthetic segments should be replaced, even if this means removing good tissue – unless less than half of one segment has been lost.
- Respect and reproduce aesthetic units wherever possible.
- Sound reconstruction requires an inner lining, adequate scaffolding and an external lining with skin of the same thickness and colour as the contralateral side.
- If the alar rim is lost, a contoured girder of cartilage needs to support the soft tissue at its edge, otherwise it will tend to retract and collapse.
- Reconstruction should only be carried out when the surgeon is sure that the tumour has been removed. Mohs' micrographic surgery should be used for morphoeiform basal cell carcinoma or squamous cell carcinoma whose margins are unpredictable. If Mohs' is not available, then it is best to wait for the histological result from paraffin sections and dress the wound in the meantime.
- Symmetry is important.
- Avoid tension but remember that excessive tissue contracts and 'bunches up'.
- A composite cartilage graft can rarely replace a whole aesthetic unit and its skin quality is often different once it has bedded in and fibroblasts have led to some contracture.

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CHAPTER
86

PINNAPLASTY

Victoria Harries and Simon Watts

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SEARCH STRATEGY

The data in this chapter are based largely on the authors' personal experience as surgeons and teachers. Pinnaplasty techniques are extensively described in textbooks of operative surgery.

BACKGROUND

'Prominent ears' is a common presentation to the paediatric ENT clinic, and represents the commonest congenital deformity of the ear with an incidence of approximately 5–6%.[1] They can be associated with severe psychological distress and consequently affect academic performance and social development.[2] It is therefore important to address any associated psychological issues as well as manage the patients' and parents' expectations when discussing the potential outcome of surgery.

There is a spectrum of ear defects that require the surgeon to tailor the consultation and operative procedure to the individual but, as an umbrella term, pinnaplasty is the surgical procedure undertaken to correct this benign deformity.

The timing of surgery remains controversial. Some surgeons advocate operating on children as young as 3 years old in order to manage the condition prior to any psychological distress[3] while others argue that the individual should be able to give informed consent before undergoing treatment.

Since Dieffenbach first performed the procedure in 1845,[4] more than 200 different techniques of pinnaplasty have been described in the literature, indicating that no single approach is a 'panacea for all ills'. In 1968, McDowell thus proposed the main objectives for a successful pinnaplasty, enabling surgeons to blend various techniques and approaches (**Box 86.1**).[5]

ANATOMY

The external ear develops from the first and second branchial arches during the 6th week of gestation. The six hillocks of His rotate and fuse to form the pinna (**Figure 86.1**).

The aesthetically normal auricle lies with its long axis tilted posteriorly by 15–20 degrees. The top of the auricle is level with the eyebrow, and its width is approximately 60% of its height (range = 5.5–6.5 cm). A normal pinna

BOX 86.1 Objectives for a successful pinnaplasty

- Elimination of the protrusion in the upper third of the ear.
- The helical fold should be parallel to the antihelical fold but visible when viewing the patient from the front.
- The helix should have a smooth and regular contour.
- The post-auricular sulcus should not be distorted.
- The auricle should be an appropriate distance away from the mastoid.
- The difference between both auricles should be within 3 mm.

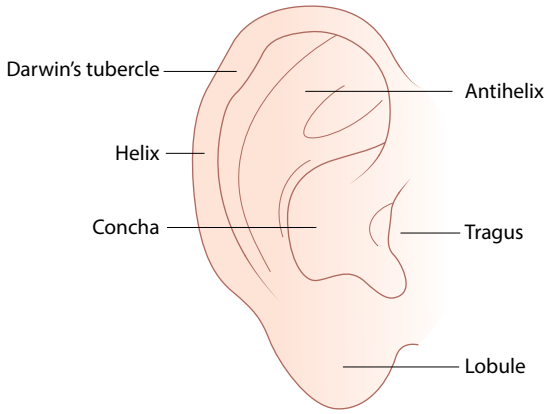

Figure 86.1 Anatomy of the pinna. (Based on a drawing by Mr Dutta, Pembury Hospital, Tunbridge Wells, UK.)

has an auriculocephalic angle of 25 degrees while protruding ears have an auriculocephalic angle greater than 40 degrees (**Figure 86.2**).

Prominent ears are an example of first-degree dysplasia, according to the classification of auricular deformities as first described by Weerda in 1988 (**Table 86.1**).[6]

Prominent ears are commonly due to one or a combination of the following defects:

- underdevelopment of the antihelical fold
- hypertrophy of the conchal bowl
- prominent lobule.

The constricted ear deformity appears as a small but prominent ear due to the small circumference of the helical rim. Stahl's ear deformity consists of an additional crus which transverses the scapha.

CONSERVATIVE METHODS

A number of non-surgical techniques have been developed for the treatment of protruding ears.

Simple moulding or splinting devices can be considered in children up to 6 months old. The high levels of oestrogen during the neonatal period allow for the cartilage to be more malleable and therefore respond to non-operative methods. The effectiveness of treatment is directly influenced by the age of the child and therefore referral of neonates with external ear deformities should be encouraged. Satisfactory results can be seen in up to 90% of patients if treatment is started within the first few days of life.[7]

OPERATIVE TECHNIQUES

Pinnaplasty can be performed under local anaesthetic or general anaesthetic as a day-case procedure although, with most patients being children, general anaesthetic is usually the preferred option.

Before surgery takes place, it is helpful to have at least two consultations with the patient/parents to confirm the need for surgery and photographs are essential for preoperative planning and for medicolegal purposes.

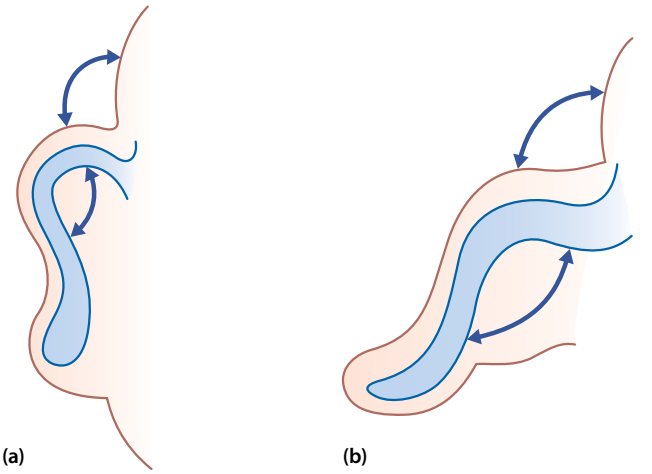

Figure 86.2 Anthropometric evaluation of a normal pinna. (Based on a drawing by Mr Dutta, Pembury Hospital, Tunbridge Wells, UK.)

TABLE 86.1 Classification of auricular deformities

Degree of dysplasia	Definition (example)
1st degree	All anatomical features present but minor≈deformities noted (prominent ears, macrotia, Stahl's ear)
2nd degree	Some anatomical features missing (cup ear, constricted ear)
3rd degree	No recognizable anatomical features (atresia)

Formation of the underdeveloped antihelical fold

Two techniques have defined the pinnaplasty operation and can be used in isolation or in combination:

- cartilage sparing/suturing technique
- cartilage excising/scoring technique.

At the start of the operation, the neo-antihelix is created by holding the helix against the mastoid. Each side of the neo-antihelix is then marked with methylene blue needle markings (**Figure 86.3**).

An elliptical skin incision is made in the posterior sulcus, which is then excised to expose the perichondrium (**Figure 86.4**).

The tattoo markings are identified posteriorly (**Figure 86.5**), and are used as landmarks for cartilage suturing or excising.

Mustardé first described the cartilage sparing/suturing technique in 1963.[8] Three or four non-absorbable mattress sutures are placed through the auricular cartilage and perichondrium using the methylene blue markers for precise placement (approximately 1 cm wide and 1 cm apart), thereby creating the new antihelical fold (**Figure 86.6**).

This technique reduces the trauma to the cartilage and, as a result, post-operative auricular irregularities rarely occur. It is widely considered to be an appropriate technique in young children with soft and malleable auricular cartilage.

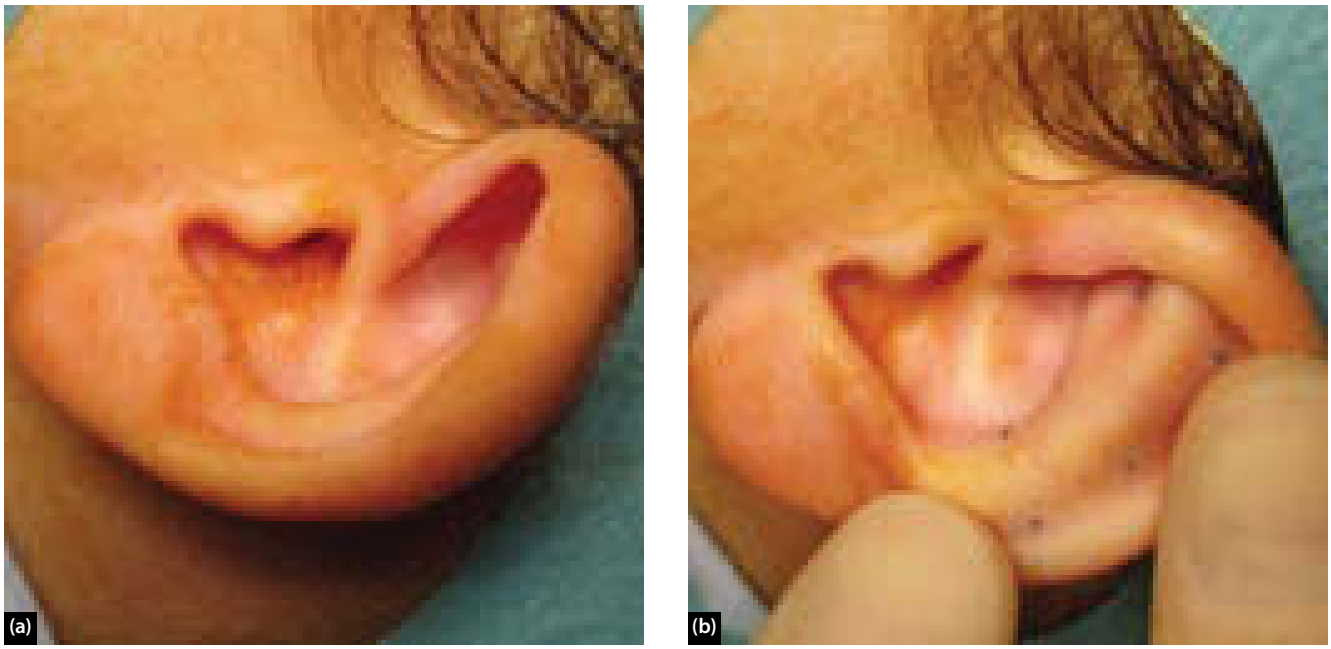

Figure 86.3 (a) A prominent ear and **(b)** the neo-antihelix with methylene blue markings.

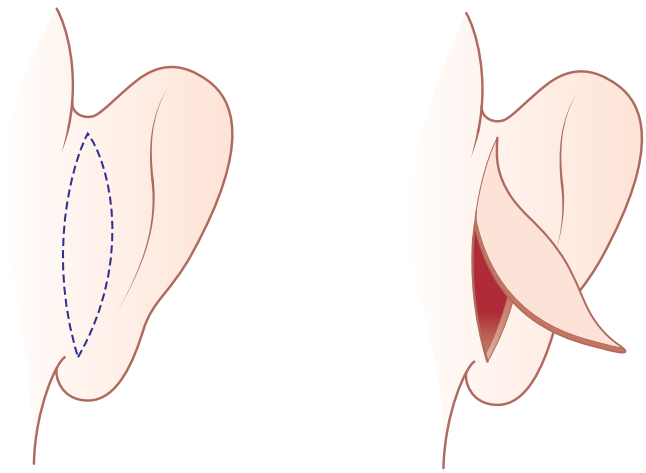

Figure 86.4 Postauricular elliptical skin excision. (Based on a drawing by Mr Dutta, Pembury Hospital, Tunbridge Wells, UK.)

It is advisable to use a non-absorbable suture such as Gore-Tex® to achieve a long-lasting result but with a minimum of reaction from the surrounding tissue (**Figure 86.7**).

Stenström described one of the initial cartilage incising/scoring techniques.[9] The scapha cartilage is incised in a 'C' shape and dissected off the anterior skin and perichondrium. The cartilage is then scored by making parallel incisions caudally from the inferior crus, which allows the antihelical fold to be developed. This technique can be used even when the cartilage is thicker in older individuals. With this technique, there is a greater risk of haematoma formation and infection due to significant skin elevation so intra-operative haemostasis and post-operative dressings are vital to prevent complications.

Usually, a combination of the two techniques allows for the disadvantages of the individual techniques to be minimized, thus reducing the potential for complications.

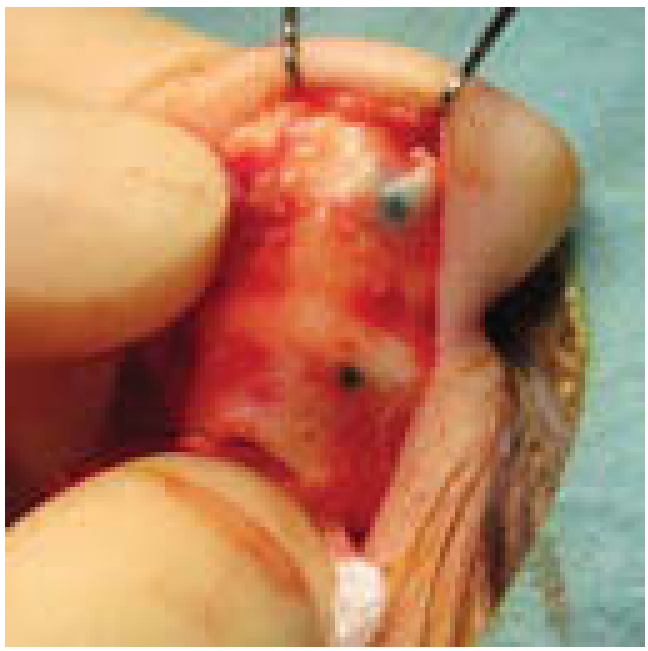

Figure 86.5 Methylene blue markings on the posterior aspect of auricular cartilage.

Additional techniques can be used as an adjunct to the conventional techniques. For example, a laterally based posterior auricular dermal flap or a bilateral fascioperichondrial flap can be used to prevent suture extrusion and decrease the rate of recurrence.

Without any particular 'gold-standard' procedure, novel techniques are continuously being developed, including cartilage-sparing methods without the use of sutures, and non-transfixing full-thickness incisions through the helix and antihelix that break the existing cartilaginous mould and therefore allow reshaping.

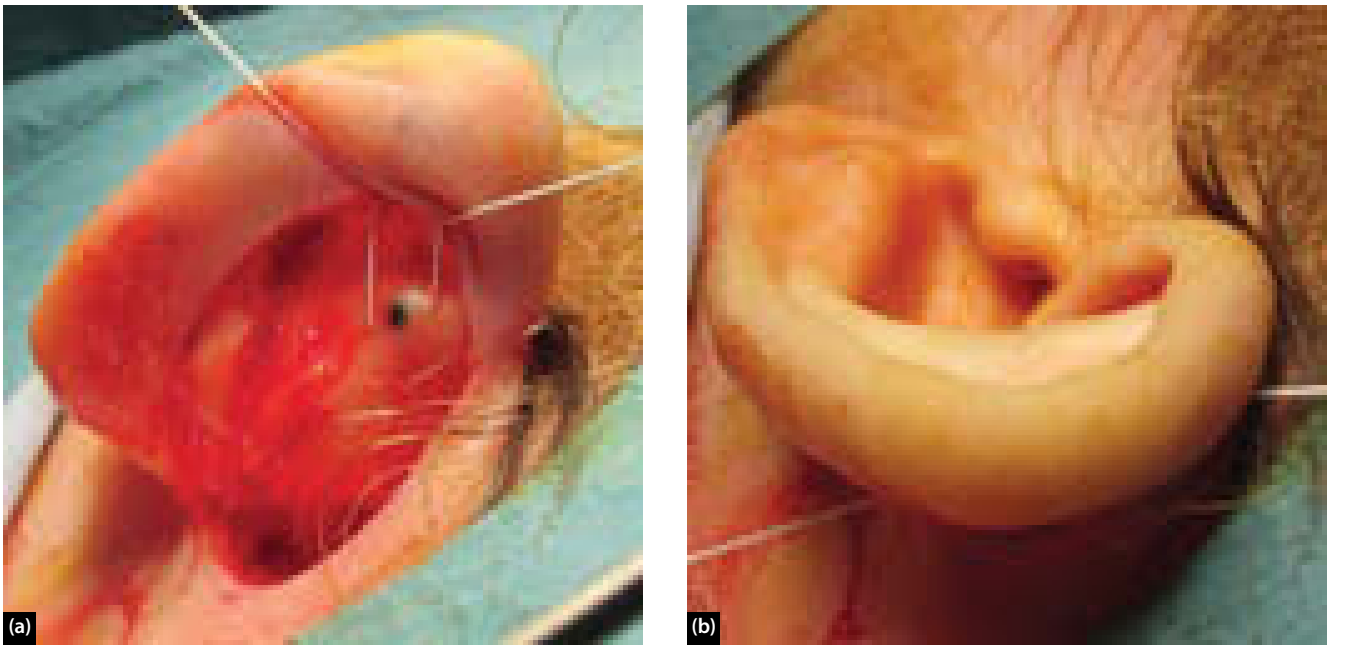

Figure 86.6 Mustardé suture.

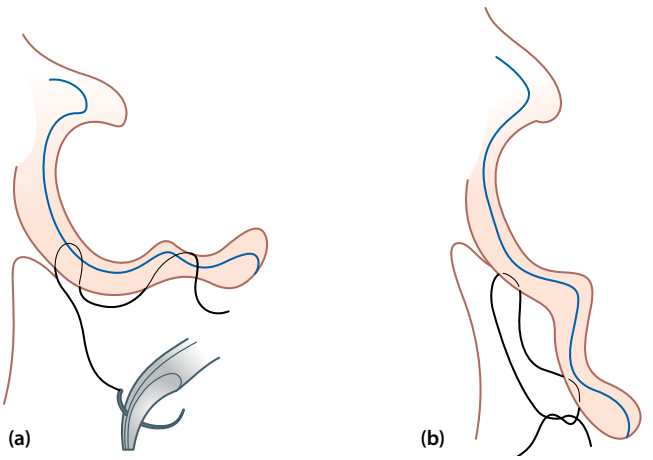

Figure 86.7 Technique of a Mustardé suture.

Correction of the conchal bowl hypertrophy

The angle between the concha and the mastoid can be reduced by a suture technique first described by Furnas in 1968 (**Figure 86.8**).[10] Care should be taken when placing the mastoid portion of the suture as placing it too close to the external ear canal may narrow the meatus when the suture is tied.

If the concha depth is more than 2.5 cm, excision of a full-thickness crescent of cartilage should be considered to correct the deformity, ideally being taken from the region of the conchamastoid sulcus.

Reconstruction of the lobule

A separate incision is made on the lobule to allow for a 'fishtail', 'wedge' or 'W-shaped' skin excision. The lobule can be repositioned by placing Goulian sutures (sutures that include postauricular skin, mastoid periosteum and posterior aspect of the lobule), therefore setting the lobule back towards the mastoid.

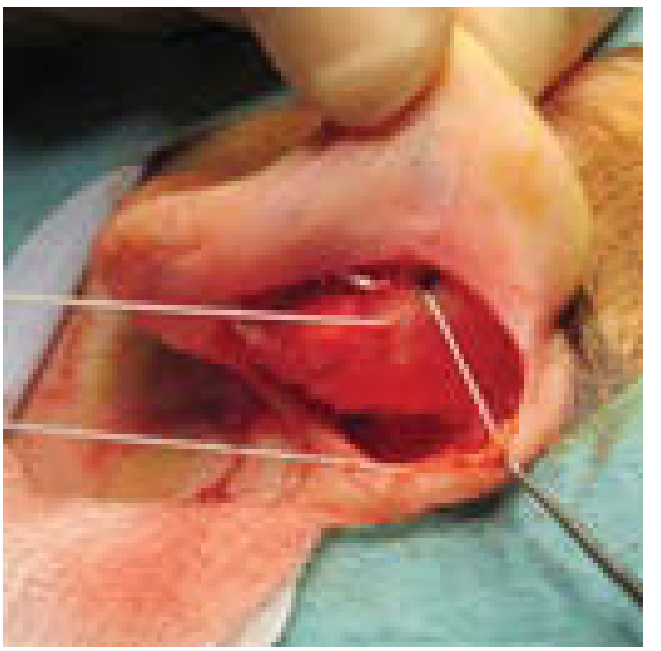

Figure 86.8 Furnas suture.

Other deformities

STAHL'S EAR DEFORMITY

The Kaplan and Hudson technique describes an incision being made along the helical rim and cartilage being

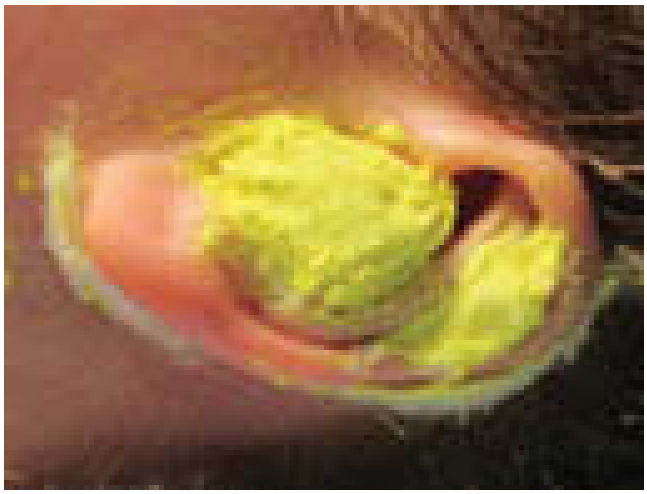

Figure 86.9 BIPP-soaked cotton wool dressing.

dissected off the skin. The affected cartilage, the extra crus, is excised and the skin is closed directly.

CONSTRICTED EAR DEFORMITY

The cup ear deformity requires elongation of the helical rim to allow the pinna to lie flat. An incision is made along the helical rim and the crus of the helix is fully mobilized and then advanced out of the concha. A standard pinnaplasty technique is then applied.

The postauricular wound can be closed with absorbable sutures, thus negating the need for removal (useful in younger children). A dressing such as BIPP-soaked cotton wool or paraffin gauze is applied to either side of the new antihelical fold and conchomastoid areas to reduce haematoma formation (**Figure 86.9**) followed by a dressing of heavy cotton wool and a crepe head bandage.

POST-OPERATIVE CARE

Head bandages in the post-operative period help to keep the dressings in place and also protect the ears. There is, however, no evidence to suggest that there is any clinical benefit conferred after 48 hours. Keeping the head up tends to reduce oedema.

COMPLICATIONS

- **Haematoma** is an early complication following pinnaplasty. It requires immediate evacuation to prevent necrosis of the cartilage. It is often signified by uncontrolled pain.
- **Infection** is a rare complication following pinnaplasty but requires early antibiotics in order to prevent chondritis and permanent deformity.
- **Keloid scarring** is a recognized complication of pinnaplasty, and patients and their families should be warned about this possibility.
- **Problems with sutures** can occur; they can extrude, and cause granulomas and hypertrophic scar formation.
- **Recurrence.** The rate of revision surgery is approximately 6% due to the pinna returning to its pre-operative position.
- **Overcorrection** is the most common complication of pinnaplasty and can lead to asymmetry or further deformity.

CONCLUSION

Many of the techniques for the correction of prominent ears are successful in achieving high satisfaction rates, despite significant variations in the techniques. Each technique has its own advantages and risks. The key to pinnaplasty is an awareness of each technique and applying the appropriate technique(s) to each individual case.

KEY POINTS

- 'Prominent ears' represents the commonest congenital deformity of the ear.
- 'Moulding' or 'splinting' is highly effective if commenced early and may avoid the need for surgery.
- Good quality pre-operative photography is an essential part of treatment planning.
- Timing of surgery varies, but most surgeons and parents prefer correction before the child goes to school or in the early years at school.
- Several operative techniques are available, each with benefits and drawbacks.
- Over-correction and asymmetry may lead to poor outcomes.

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CHAPTER 87

BLEPHAROPLASTY

Brian Leatherbarrow

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Upper eyelid blepharoplasty 1209
Lower eyelid blepharoplasty 1214
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SEARCH STRATEGY

Data in this chapter may be updated by a PubMed search using the keywords: cosmetic eyelid surgery, blepharoplasty, brow lift, dermatochalasis, midface lift and blepharoplasty complications.

INTRODUCTION

The term blepharoplasty is used to refer to an operation in which redundant tissues including skin, or skin and muscle, are excised from the eyelid, and in which fat may be excised, sculpted or repositioned. The appearance of the eyelids, and the periorbital region, plays a pivotal role in maintaining facial harmony through expression of human character, mood and emotions, and a successful outcome from this surgery requires great attention to detail.

A blepharoplasty can be performed for both functional and aesthetic reasons. A functional blepharoplasty aims to restore normal function and appearance to an eyelid that has been altered by trauma, infection, inflammation, degeneration, neoplasia or a developmental anomaly. A cosmetic blepharoplasty aims to improve the appearance of eyelid tissues that are histologically and functionally normal.

Patients who enquire about, or who are referred for, upper and lower eyelid blepharoplasty tend to present with a variety of aesthetic and functional complaints (**Figure 87.1**). These include:

- a tired look
- hooding of the upper eyelids
- 'drooping' of the upper eyelids
- 'eye bags'
- skin wrinkling
- skin folds
- a visual field defect
- headaches
- irritation of the upper eyelids
- lower lid 'dark circles'.

Female patients often complain of the inability to place make-up on the upper eyelid.

An upper eyelid blepharoplasty may involve the removal of skin alone, or skin and orbicularis muscle, or this may be combined with the removal or sculpting of herniated orbital fat. Occasionally an upper eyelid blepharoplasty will only involve the removal, sculpting or redraping of fat. The procedure may be combined with an eyebrow lifting or blepharoptosis procedure. The procedure may be performed for functional reasons to improve a patient's visual field restricted by dermatochalasis, or to improve symptoms of irritation from redundant skin hanging over the upper eyelid lashes, and/or for cosmetic reasons.

A lower eyelid blepharoplasty is more frequently performed for cosmetic reasons alone and may also involve the removal of skin and muscle alone or this may be combined with the removal and/or repositioning of herniated orbital fat, the resuspension of a ptotic orbicularis oculi muscle, a lateral canthal suspension, an orbital decompression procedure for thyroid eye disease or a midface or suborbicularis oculi fat (SOOF) lift. It may also be combined with skin-rejuvenating procedures (e.g. laser skin resurfacing, a chemical peel or the post-operative injection of dermal fillers).

Blepharoplasty is one of the most commonly performed cosmetic operations.

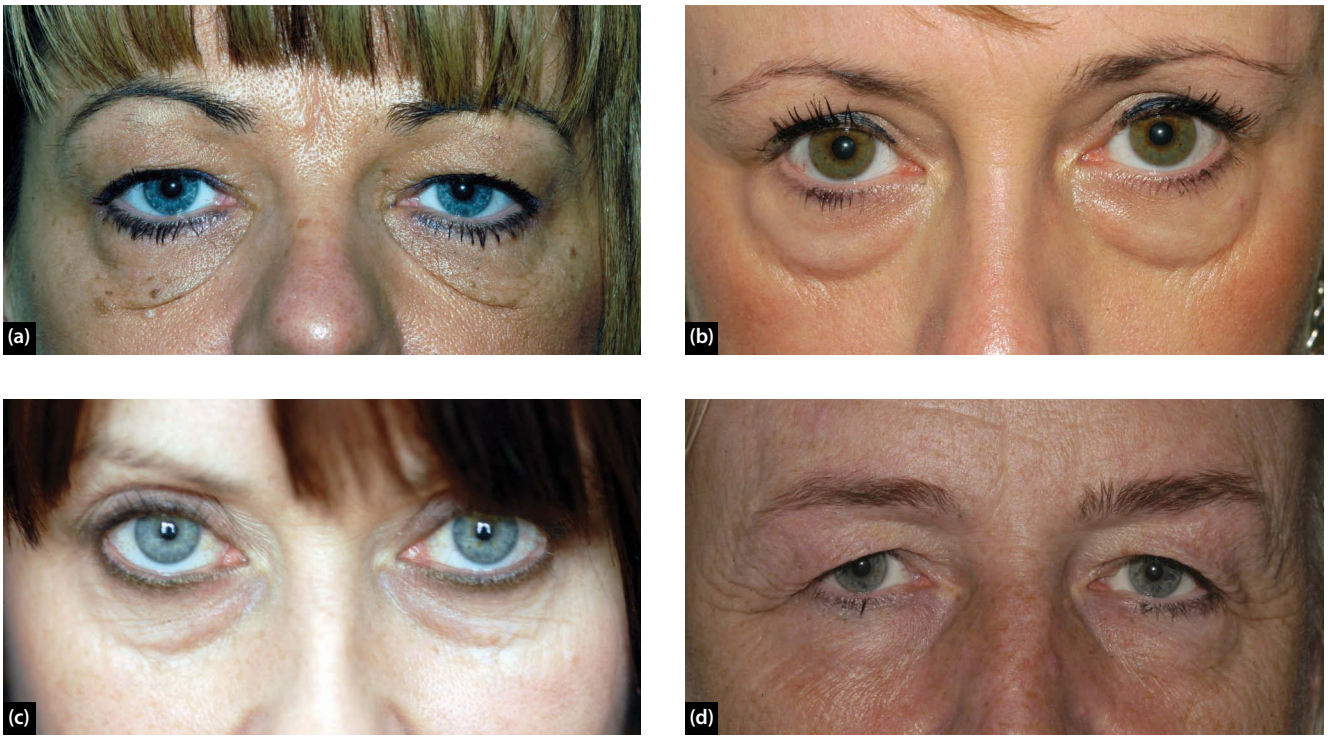


Figure 87.1 **(a)** A patient complaining of hooded upper lids with an inability to place make-up, and loose folds of skin in the lower eyelids. She was a heavy smoker. **(b)** A patient complaining of unsightly lower eyelid 'bags'. **(c)** A patient complaining of lower eyelid 'dark circles' creating a 'tired look'. **(d)** A patient complaining of a 'blinkered feeling' with a restriction of her visual fields.

APPLIED ANATOMY

A thorough understanding of the surgical anatomy of the eyebrows, eyelids and midface is essential prior to performing a blepharoplasty. This anatomy should be carefully reviewed. Additional aspects of surgically relevant anatomy are presented below.

The upper eyelids

The palpebral aperture is almond-shaped, with the lateral canthal angle lying slightly higher than the medial canthal angle. The lateral canthal angle is generally slightly higher in females than males and lies approximately 5 mm from the lateral orbital margin (**Figure 87.2**). The upper eyelid skin crease is usually approximately 5–6 mm above the lash line in males and 7–8 mm in females.

The distance between the inferior aspect of the eyebrow and the upper lid skin crease on downgaze should be approximately two-thirds of the distance from the inferior aspect of the eyebrow to the eyelid margin. Likewise, the distance from the skin crease to the eyelid margin in downgaze should be one-third of the distance from the inferior aspect of the eyebrow to the eyelid margin (**Figure 87.2**).

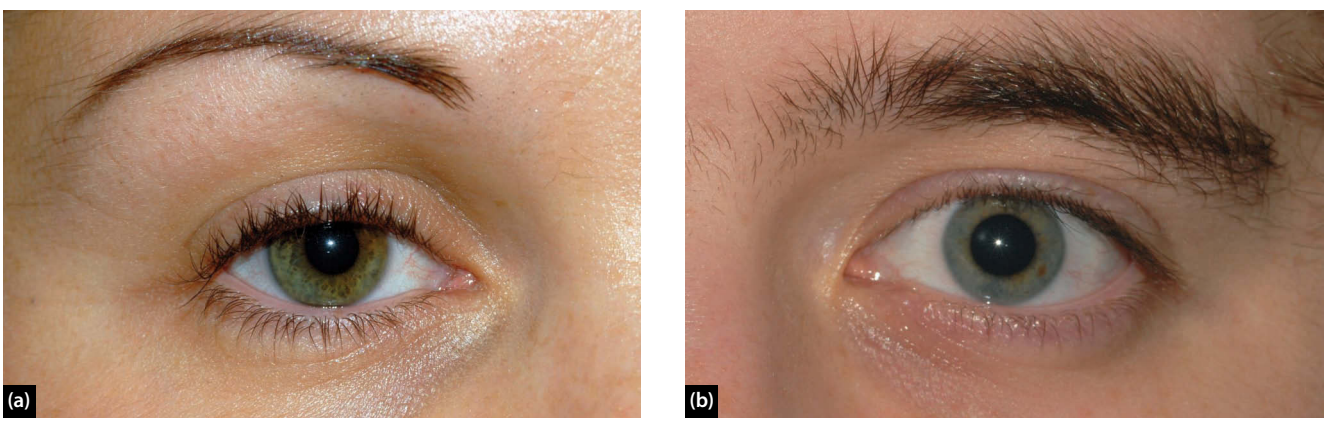


Figure 87.2 **(a)** The typical topographical anatomy of the periorbital region of a young female showing a skin crease at 6–7 mm above the eyelid margin and an arched eyebrow with the temporal aspect of the eyebrow lying at a higher position than the medial aspect. Note that the eyebrow has been plucked. It is important to take this into consideration when making measurements for skin resection. **(b)** The typical topographical anatomy of the periorbital region of a young male showing a skin crease at 5–6 mm above the eyelid margin and a flatter eyebrow contour.

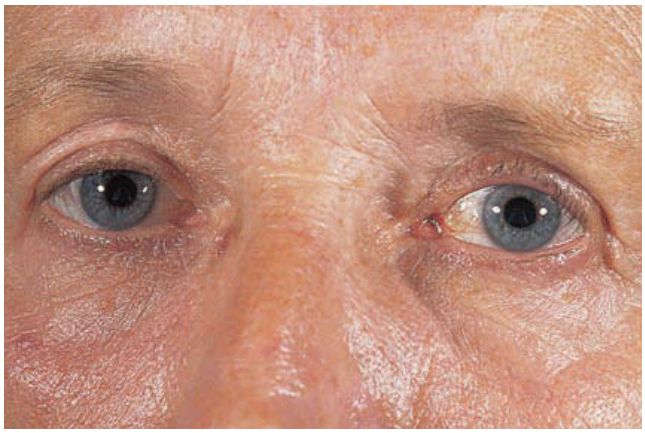


Figure 87.3 A patient following an excessive resection of her left upper eyelid skin with worsening of her brow ptosis. She also has asymmetry of the upper eyelids and brows post-operatively.

In general, a minimum distance of 10–12 mm should be left between the inferior aspect of the eyebrow and the upper eyelid skin excision marking when performing an upper lid blepharoplasty and, again in general, approximately 20 mm of skin should be left between the inferior aspect of the eyebrow and the eyelid margin.

It is important to maintain these dimensions. If an excessive amount of upper eyelid skin is removed, reducing the distance from the skin crease to the brow in the presence of a brow ptosis, an unsatisfactory result will occur, with the appearance of the brow being attached to the eyelashes (**Figure 87.3**). This may also cause lagophthalmos (**Figure 87.4**).

It is important to differentiate prolapsed preaponeurotic fat from retro-orbicularis oculi fat (ROOF) that has descended into the upper eyelid (**Figure 87.5**). This may give rise to the appearance of upper eyelid 'fullness' (**Figure 87.6**). Although this descended fat can

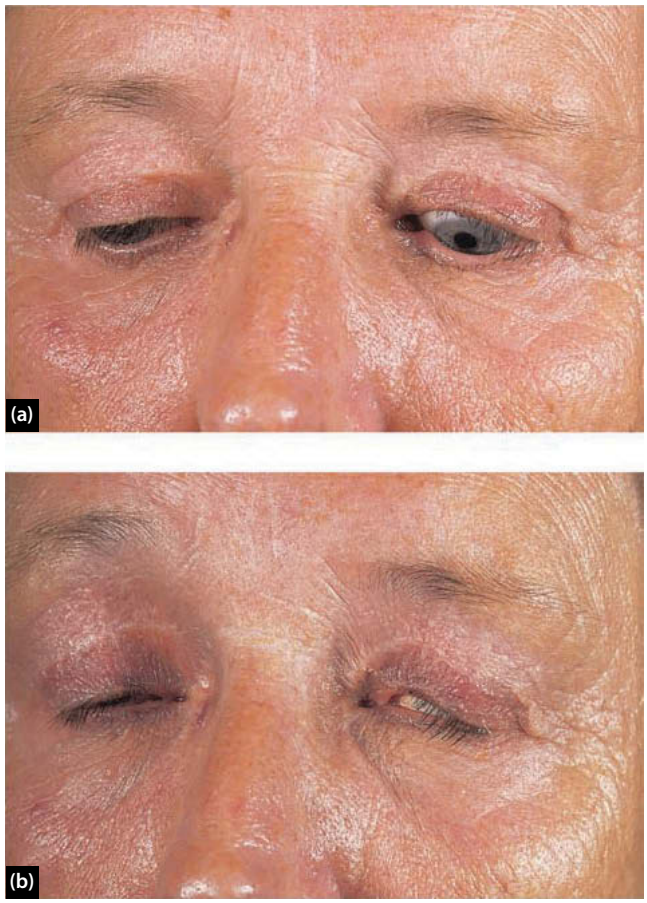


Figure 87.4 (a) The same patient as in Figure 87.3 demonstrating severe lag on downgaze. **(b)** The same patient demonstrating lagophthalmos on attempted passive eyelid closure. She also shows very poor placement of the upper lid skin incisions and only 5–6 mm of skin between the left upper lid incision and the lowermost position of the eyebrow centrally.

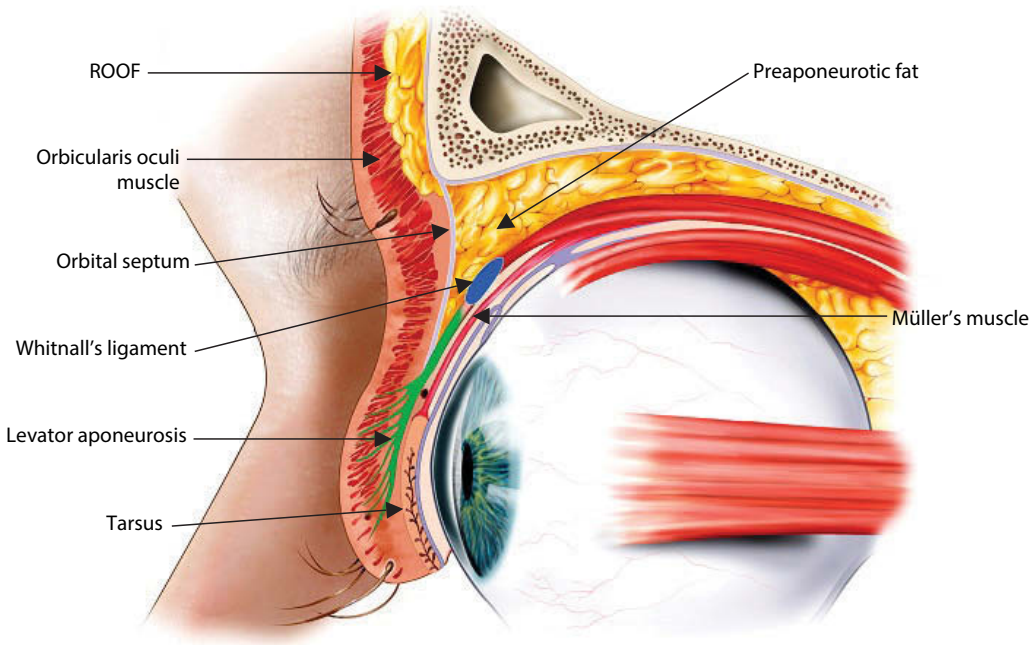


Figure 87.5 Diagram illustrating the position of preaponeurotic fat.

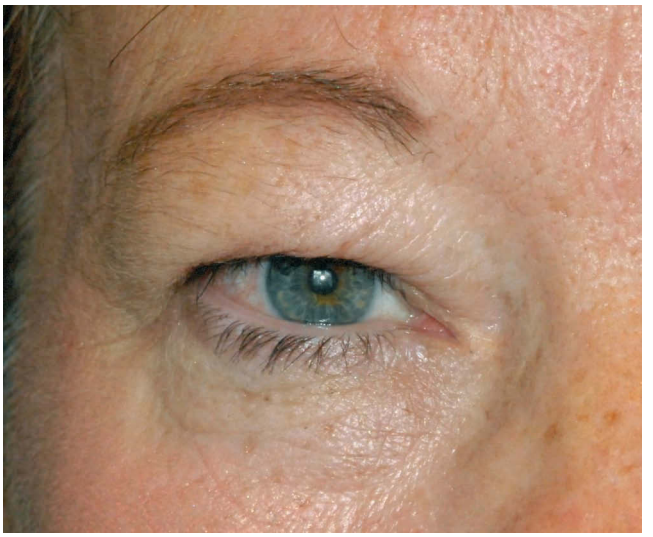


Figure 87.6 Fullness of the upper eyelid due to descent of the retro-orbicularis oculi fat (ROOF).

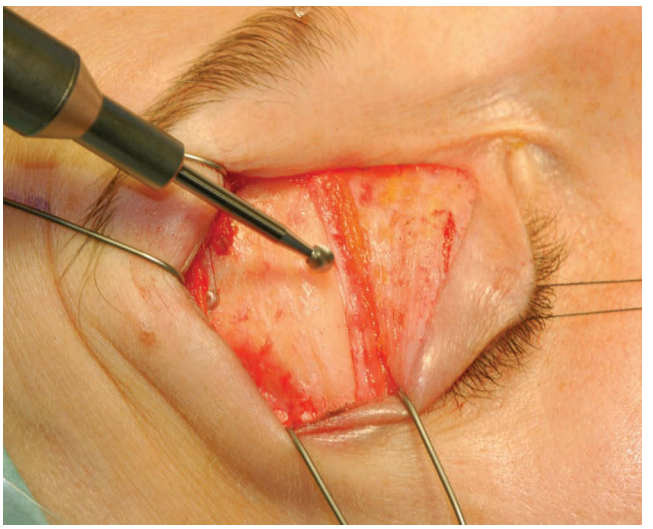


Figure 87.7 A burr is being used to reduce the prominence of the supraorbital margin in this patient.

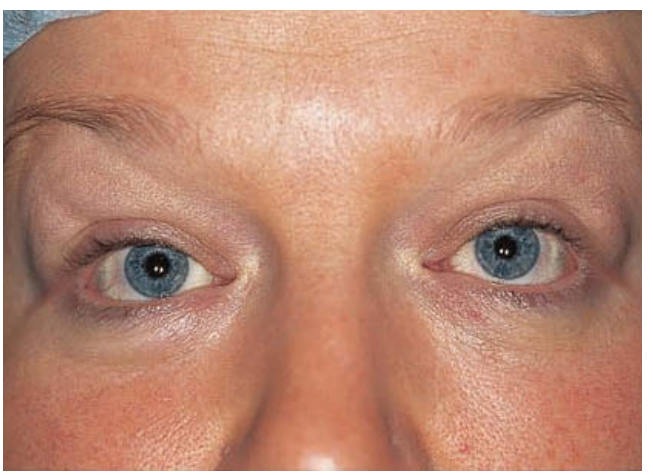


Figure 87.8 A patient with bilateral lateral upper eyelid swellings due to spontaneous lacrimal gland prolapses.

be debulked, it is preferable to reposition it as part of a browlift procedure.

Some patients have very prominent superolateral bony margins that can also contribute to upper eyelid 'fullness'. This can be exposed and reduced with the use of a burr during the course of an upper eyelid blepharoplasty (**Figure 87.7**).

Subcutaneous thickening of this area in the dysthyroid patient must be recognized. This may not be amenable to improvement by standard blepharoplasty surgery. An overly aggressive upper eyelid blepharoplasty in a patient with thyroid eye disease can markedly worsen symptoms of corneal exposure.

It is important to recognize a prolapsed lacrimal gland that may be responsible for lateral upper eyelid 'fullness' or swelling (**Figure 87.8**). Prolapsed glands can be repositioned during the course of an upper eyelid blepharoplasty by suturing the gland to the periorbita of the lacrimal gland fossa (**Figures 87.9–87.11**).

Some patients develop orbital fat atrophy which creates an upper eyelid sulcus defect. The removal of preaponeurotic fat in such patients should be avoided to prevent a post-operative 'cadaveric' appearance. A prolapsed medial fat pad in such a patient can be debulked and the fat transplanted to lie evenly in the preaponeurotic space. In general, the removal of fat from the upper eyelid should be avoided in the majority of patients.

'Fullness in the medial aspect of the upper eyelid may be caused by a medial eyebrow ptosis. Elevation of the brow, or the use of botulinum toxin injections in the glabella, can be more successful at addressing this problem. Incisions in this area can leave unsatisfactory scarring. It is important to avoid the temptation to 'chase a dog ear' into this area beyond the medial limit of the skin crease during an upper eyelid blepharoplasty as the subsequent scarring can be very unsatisfactory. In such patients a gentle debulking of the medial fat pad can allow the skin to redrape with a more satisfactory aesthetic result, but over-resection of fat should be avoided. The fat should not be discarded as it may be required for use in the central aspect of the upper lid or may be of use to help to treat a medial tear trough defect in the lower eyelid.

The upper eyelid skin crease represents the most superior point of attachment between the skin and the levator aponeurosis. This position is just inferior to the insertion of the orbital septum onto the levator aponeurosis. The skin crease lies at a higher level in females, approximately 7–8 mm from the lash line, compared to 5–6 mm in males. It is important not to raise the skin crease in males to avoid a 'feminization' of the eyelid appearance.

The skin crease shows racial differences. In the oriental eyelid the orbital septum attaches to the levator aponeurosis at a lower level, allowing the preaponeurotic fat to descend into the lower reaches of the eyelid, preventing the levator aponeurosis from forming a high skin crease. A great deal has been written about the oriental eyelid and the oriental blepharoplasty. However, this detail is beyond the scope of this textbook.

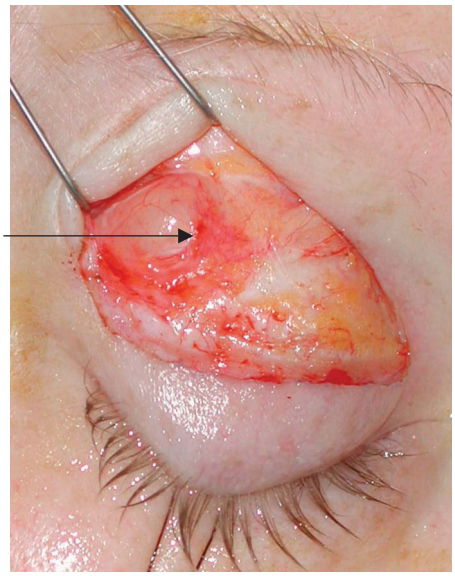


Figure 87.9 A right lacrimal gland prolapse as seen during an upper lid blepharoplasty.

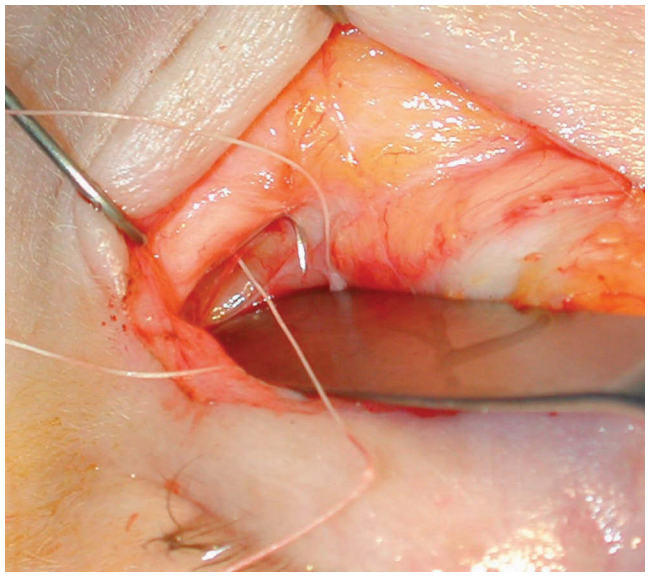


Figure 87.10 A double-armed 5-0 Vicryl suture is being placed through the periorbita of the lacrimal gland fossa.

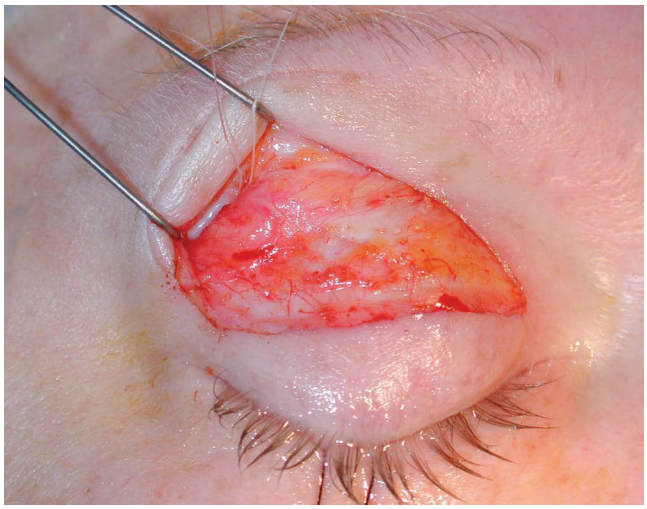


Figure 87.11 The Vicryl suture has been passed through the capsule of the lacrimal gland and tied, repositioning the gland into the lacrimal gland fossa.

The skin of the upper eyelid is very thin, without any subcutaneous fat. Beneath the skin lies the very vascular orbicularis muscle. Local anaesthetic injections should be placed immediately beneath the skin, avoiding the orbicularis muscle, to prevent the occurrence of a haematoma. Deep to the orbicularis muscle above the skin crease lies the orbital septum. This originates from the arcus marginalis along the superior orbital margin. This firm attachment can be utilized to differentiate it from the levator aponeurosis. The orbital septum is a multilayered structure with a very variable thickness.

Posterior to the septum lies the preaponeurotic orbital fat. Pressure applied to the lower eyelid can force the fat to prolapse, which helps to differentiate this from descended retro-orbicularis fat and from fatty degeneration of the levator muscle and/or Müller's muscle. The preaponeurotic fat is a key landmark in upper eyelid surgery. The levator aponeurosis lies immediately beneath it (see **Figures 87.5** and **87.12**).

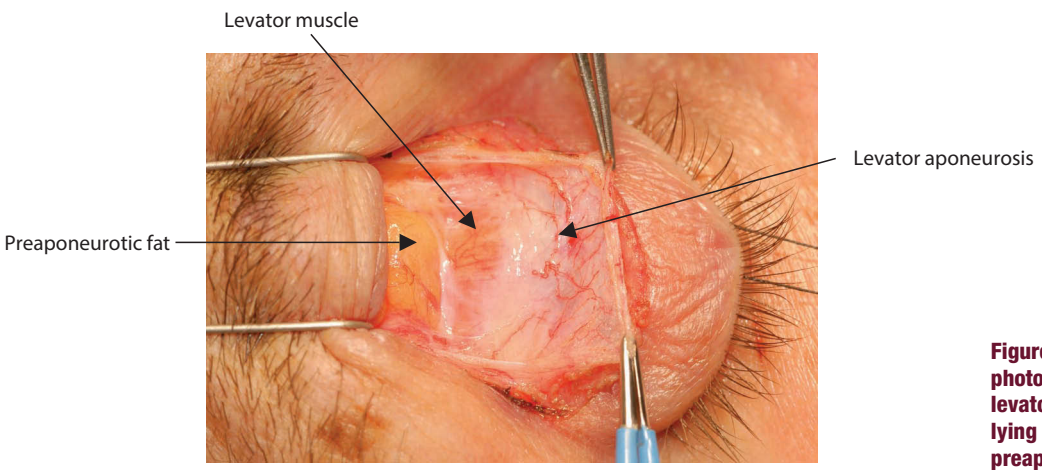


Figure 87.12 Intra-operative photograph demonstrating the levator muscle and its aponeurosis lying immediately beneath the preaponeurotic fat.

There are two main fat pads in the upper eyelid, a central pad and a nasal pad. The nasal fat pad is generally paler (**Figure 87.13**). It is extremely important to be able to distinguish the lacrimal gland from the orbital fat (**Figure 87.14**).

The levator muscle gives rise to the levator aponeurosis at the level of Whitnall's ligament. The aponeurosis inserts onto the anterior surface of the superior two-thirds of the tarsus. The medial and lateral horns of the aponeurosis insert in the region of the medial and lateral canthal tendons. The lateral horn divides the lacrimal gland into orbital and palpebral lobes. Intra-operative damage to the medial horn can give rise to a lateral shift of the tarsus with an eyelid peak lying temporal to the pupil.

Whitnall's ligament supports the levator muscle complex, acting as a fulcrum for the action of the levator muscle, and should not be disturbed during surgery. It is a variably developed structure that runs from the lacrimal gland to the region of the trochlea (**Figure 87.15**).

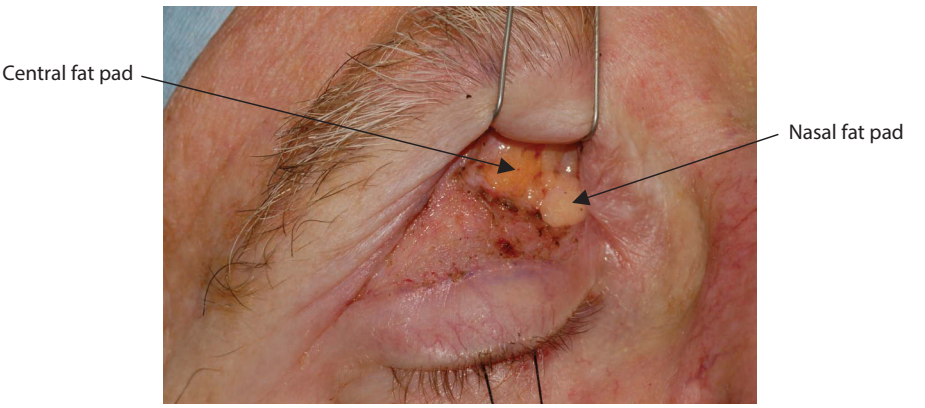


Figure 87.13 The nasal fat pad is paler than the central fat pad.

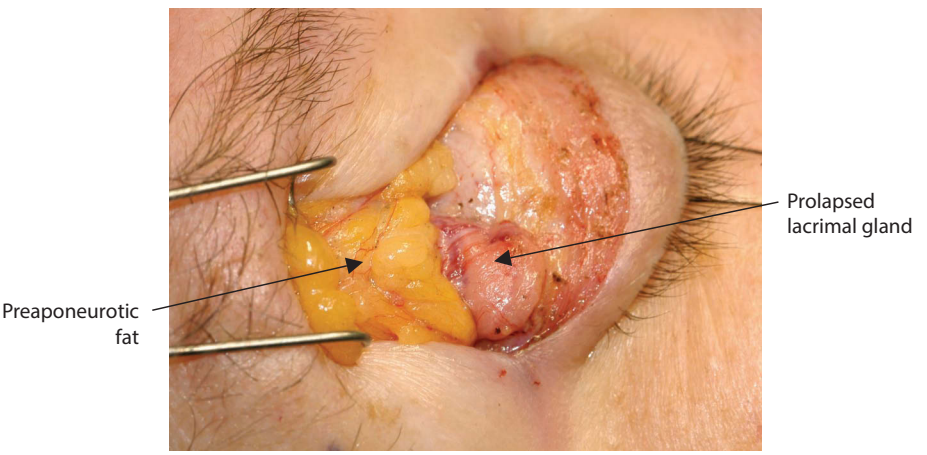


Figure 87.14 A prolapsed lacrimal gland.

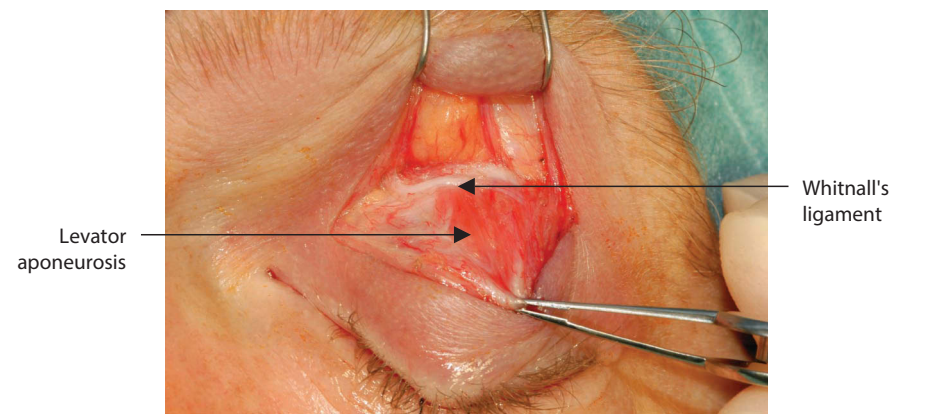


Figure 87.15 Whitnall's ligament.

The lower eyelids

The lower eyelid can be considered to consist of three lamellae:

- anterior – skin and the orbicularis oculi muscle
- middle – the orbital septum and the inferior eyelid retractors
- posterior – the tarsus and conjunctiva.

The lower eyelid skin crease is variable but is usually situated approximately 4–5 mm below the eyelid margin. The lateral canthal angle normally sits approximately 1 mm higher than the medial canthal angle.

The orbicularis oculi muscle is immediately deep to the skin of the lower lid. This muscle extends from just below the ciliary margin, past the inferior orbital rim and onto the cheek. Ptosis of the orbicularis oculi muscle commonly occurs over time and is responsible for the typical appearance of the malar crescent or malar mound in the aged face (see **Figure 87.23**).

Deep to the orbicularis oculi muscle lies the orbital septum, which serves to retain orbital fat within the orbit. The septum is composed of inelastic fibrous tissue. Atrophy of the septum with age permits orbital fat to herniate anteriorly creating typical lower lid 'bags' (see **Figure 87.1b**). The suborbicularis fascia, a plane of loose, fibrous connective tissue, lies between the orbicularis and orbital septum and provides a very good, relatively bloodless, dissection plane. The orbital septum extends from the inferior border of the tarsus to fuse inferiorly with the periosteum of the infraorbital margin. This inferior attachment of the orbital septum to the periosteum, where there is a condensation of tissue, is referred to as the arcus marginalis (**Figure 87.16**).

The arcus marginalis is strongest and best defined medially, where it attaches to the anterior lacrimal crest. As it extends laterally, it thins and weakens. It also assumes a more inferior and anterior insertion; thus, medially, it runs along the inner aspect of the rim but, laterally, it attaches approximately 2 mm inferior to the rim on the facial aspect of the zygomatic bone.

The tarsus in the lower eyelid is approximately 4–5 mm in height. The lower eyelid retractors are analogous to the levator aponeurosis in the upper eyelid. The smooth inferior tarsal muscle is analogous to Müller's muscle in the upper eyelid. The lower eyelid retractors, collectively referred to as the capsulopalpebral fascia, run from the inferior rectus muscle and split to envelop the inferior oblique muscle. This fascia then inserts into the inferior border of the tarsus (**Figures 87.16** and **87.17**). A deep layer of the fascia attaches to the conjunctival fornix as the suspensory ligament of the fornix.

Isolated shortening of the anterior lamella of the lower eyelid results in ectropion, of the middle lamella results in eyelid retraction with scleral show (**Figure 87.18**), and of the posterior lamella results in entropion.

There are three fat compartments in the lower eyelid: medial, central and lateral. Many delicate fibrous septa invest these compartments. The fat compartments lie between the capsulopalpebral fascia and the orbital septum. As the capsulopalpebral fascia (the lower eyelid retractor)

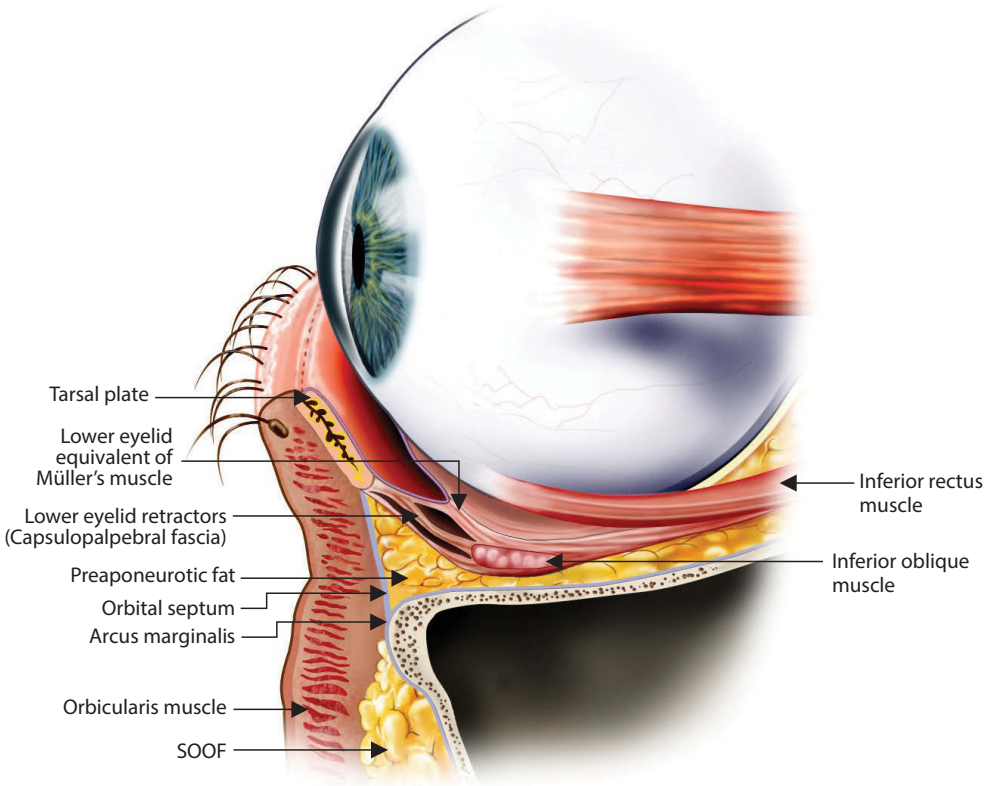


Figure 87.16 Diagram illustrating the anatomy of the lower eyelid region.

is analogous to the levator aponeurosis in the upper eyelid, the fat lying in front of the capsulopalpebral fascia can be considered to be analogous to the preaponeurotic fat in the upper eyelid. As in the upper eyelid, locating this fat is key to locating the eyelid retractor.

The inferior oblique muscle, originating from the anteromedial orbital wall, lies between and separates the medial and central fat compartments as it extends posterolaterally under the globe (**Figure 87.19**).

The arcuate expansion, an extension of the fascial sheath of the inferior oblique, continues laterally to attach to the lateral orbital rim and separates the central and lateral compartments (**Figure 87.20**). Subtle differences exist among the three orbital fat pads. The fat of the medial compartment is typically white and membranous, while that of the central and lateral compartments appears yellow and soft. The lateral fat compartment contains more septa than the medial and central compartments and is

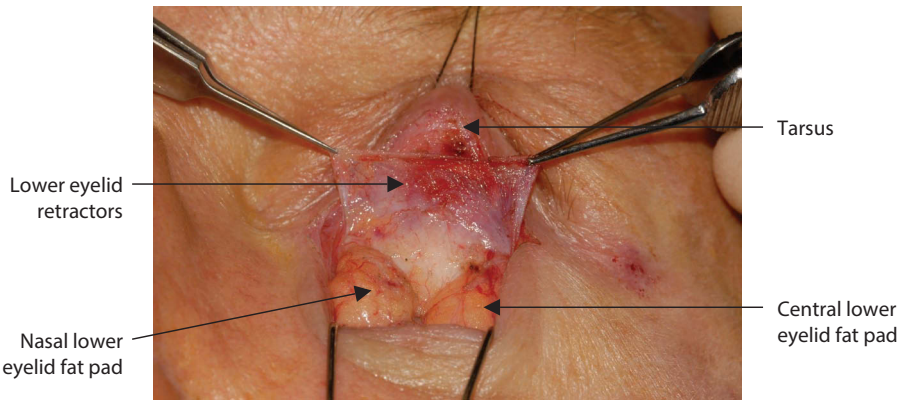


Figure 87.17 The lower eyelid retractors detached from the inferior border of the tarsus.

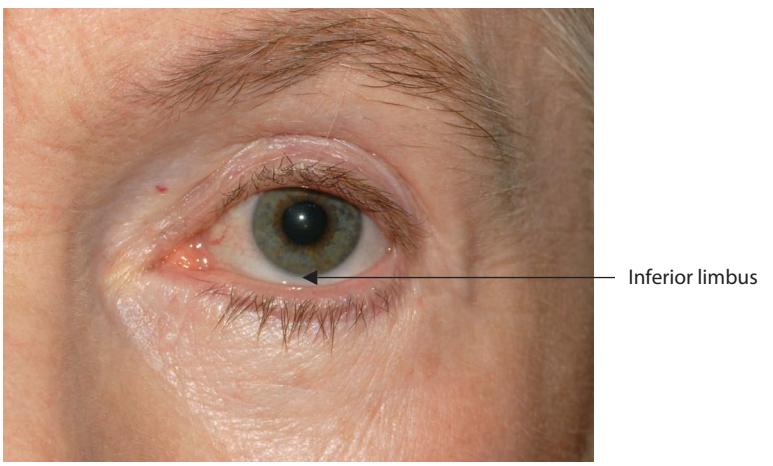


Figure 87.18 Middle lamellar scarring following a lower eyelid blepharoplasty resulting in lower eyelid retraction and scleral 'show' below the inferior limbus.

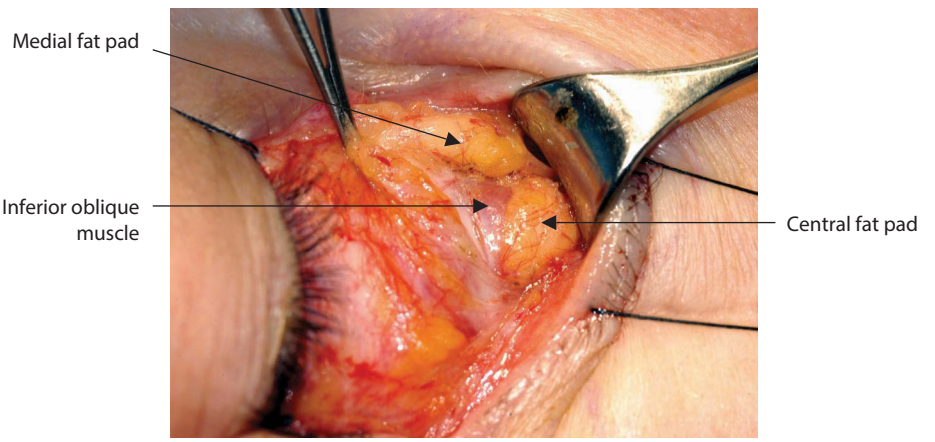


Figure 87.19 The inferior oblique muscle lying between the medial and central fat pads.

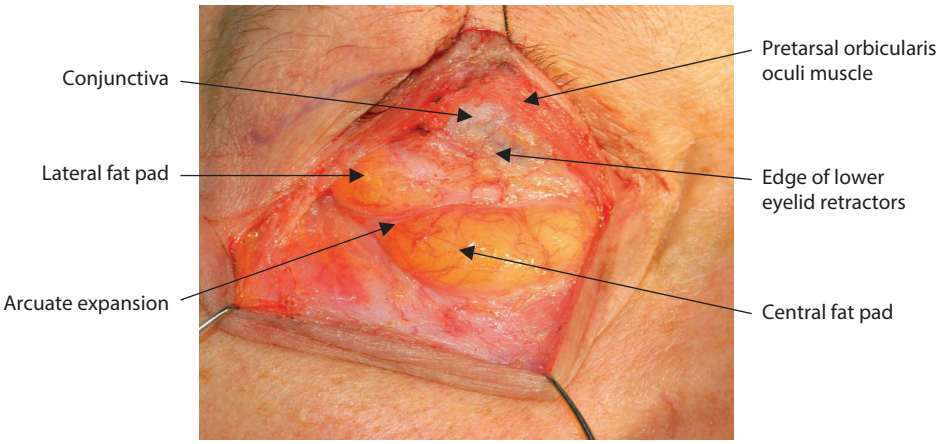


Figure 87.20 The arcuate expansion separating the central and lateral lower lid fat pads.

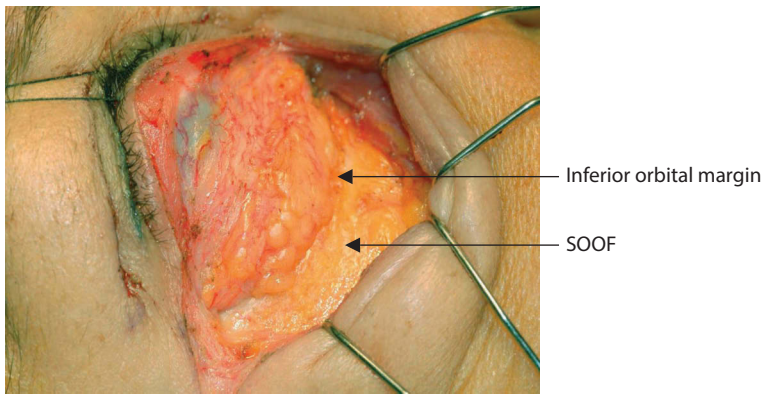


Figure 87.21 The suborbicularis oculi fat (SOOF).

therefore less prone to herniate anteriorly. It is important to note that inferior palpebral vessels travel directly through the medial fat compartment.

Fat seen below the inferior orbital margin posterior to the orbicularis oculi muscle and just anterior to the periosteum is the suborbicularis oculi fat (SOOF) (**Figure 87.21**).

With increasing age, the orbicularis oculi muscle and the SOOF move inferiorly, leading to a double convexity of the lower eyelid. The superior convexity is caused by a herniation of orbital fat through a weakened orbital septum above the inferior orbital margin (**Figure 87.22**). The orbital margin itself is responsible for the horizontal concavity and the SOOF, which has moved inferiorly, is responsible for the second convexity.

The midface

Knowledge of the anatomy of the midface is essential to the understanding of the morphological changes which occur at the lower eyelid–cheek junction with advancing age.

The prezygomatic space is a triangular space overlying the zygomatic and maxillary bones with its apex towards the nose and is limited superiorly by the orbitomalar ligament. It contains:

- fat overlying the orbital part of the orbicularis muscle
- the orbital part of the orbicularis muscle
- the SOOF
- pre-periosteal fat deep to the origin of the lip elevator muscles.

RETAINING LIGAMENTS

There are a number of retaining ligaments in the face which are condensations of fibrous connective tissue and which act to anchor the superficial tissue layers to firmer underlying structures. These ligaments are divided into true and false retaining ligaments.

- True retaining ligaments link the dermis to the underlying periosteum (zygomatic, orbital, orbitomalar and mandibular ligaments).
- False retaining ligaments link the deep facial fascia to the superficial facial fascia and the subcutaneous tissue (masseteric and platysma-auricular ligaments).

The zygomatic retaining ligament (McGregor's patch) arises from the zygomatic arch and from the body of the zygoma, passes through the superior aspect of the malar fat pad and inserts into the dermis of the overlying skin. The ligament is well-defined. The orbital retaining ligament lies over the frontozygomatic suture.

The orbitomalar ligament arises from a thickened area of periosteum a few millimetres below the inferior

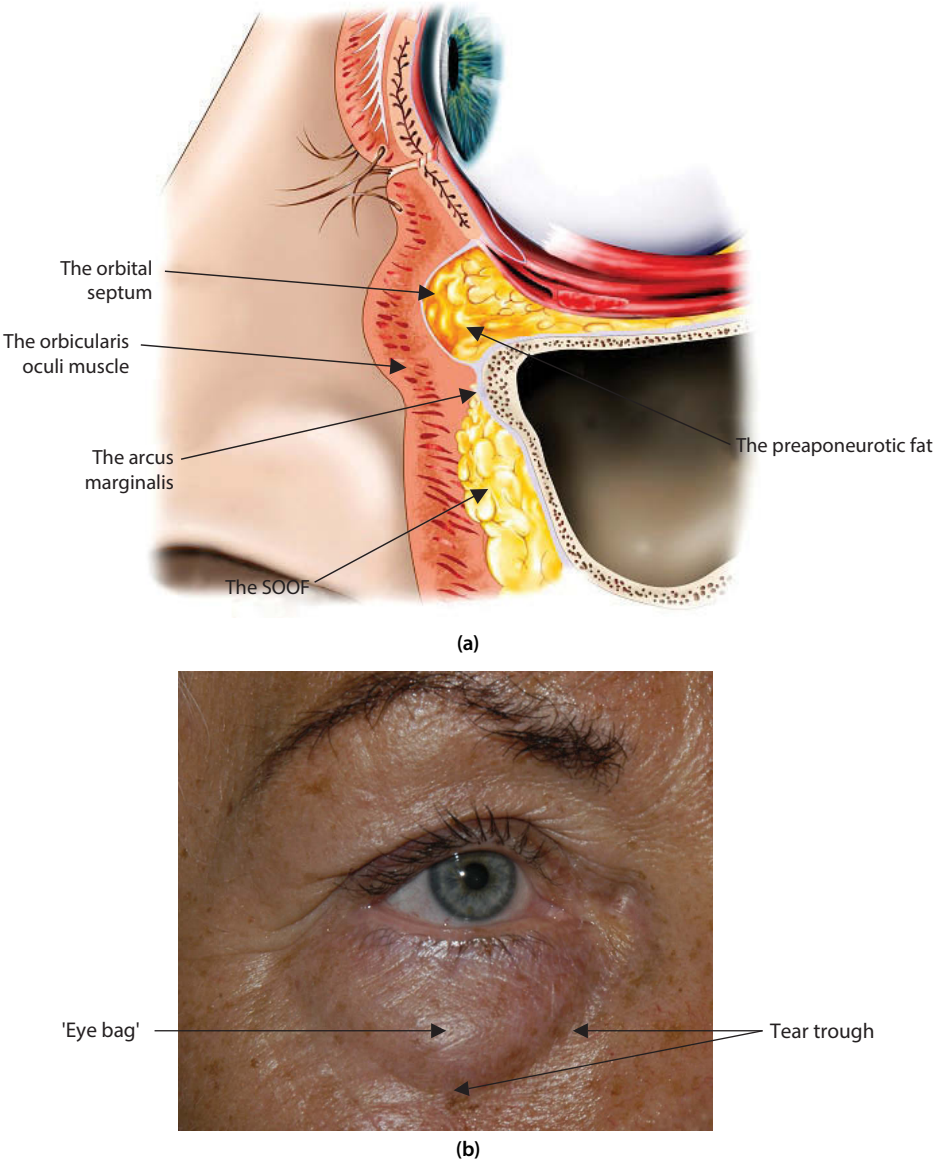


Figure 87.22 **(a)** A diagrammatic representation of bulging preaponeurotic fat through a weakened orbital septum with a secondary concavity over the inferior orbital margin responsible for the complaint of 'eyebags' and for a tear trough deformity or 'dark circle'. **(b)** A patient demonstrating the typical 'eyebag' and tear trough extending along the whole length of the inferior orbital margin.

orbital margin, and passes through the superficial musculoaponeurotic system (the SMAS) and overlying fat to insert into the dermis.

The orbitomalar ligament, the levator labii superioris and the levator alaeque nasi muscles are responsible for defining the tear trough. The tear trough extends into the upper central cheek as a triangular groove between these muscles as the malar fat descends with age.

'Malar mounds' are the result of oedema within the fat of the prezygomatic space (**Figure 87.23** below). The malar fat pad is subcutaneous, triangular and distinct from the 'malar mounds'. This fat pad contributes to the fullness of the midface. Elevation of the malar fat pad and the 'malar mounds' contributes greatly to the aesthetic appearance of the midface and can improve the appearance of the tear troughs.

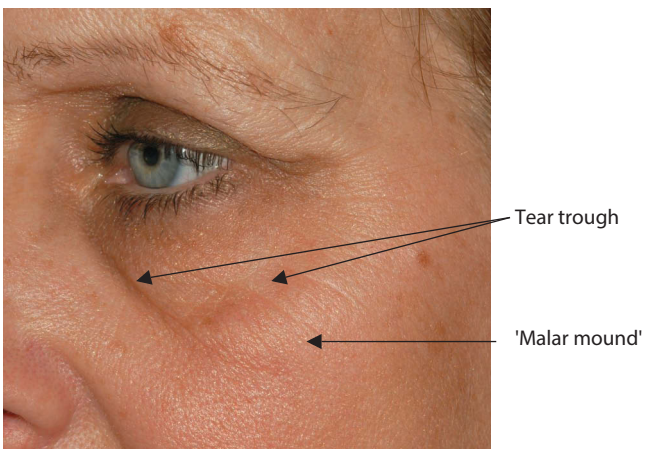


Figure 87.23 Typical age-related changes at the eyelid–cheek junction.

DERMATOCHALASIS

Dermatochalasis describes a common, physiologic condition seen clinically as sagging of the upper eyelid skin. It is typically bilateral and most often seen in patients over 50 years of age, but it may occur in some younger adults. Examination of these patients' eyelids reveals redundant, lax skin with poor adhesion to the underlying orbicularis oculi muscle. An excess fold of skin in the upper eyelid is characteristic, which obscures the normal upper eyelid skin crease which may be lost (**Figure 87.24**). This patient complained of visual field limitation and headaches towards the evening (due to frontalis muscle fatigue).

Dermatochalasis is often confused with blepharochalasis although the disorders are quite different in both their presentation and their aetiology. Blepharochalasis is a rare inflammatory condition that typically affects only the upper eyelids, and may be unilateral as well as bilateral. It occurs more often in younger patients. The condition is characterized by exacerbations and remissions of eyelid oedema, which results in a 'stretching' and subsequent atrophy of the eyelid tissue. The secondary effects of blepharochalasis include conjunctival hyperaemia and chemosis, entropion, ectropion, blepharoptosis, medial fat pad atrophy and thinning of eyelid skin.

Pathophysiology

The tissue changes seen in dermatochalasis are similar to the normal ageing changes of the skin seen elsewhere in the body. There is thinning of the epidermal tissue with a loss of elastin, resulting in laxity, redundancy and hypertrophy of the skin. The tissue changes of dermatochalasis appear to be due to repeated facial expressions combined with the effects of gravity over many years. A number of systemic disorders such as thyroid eye disease, Ehlers–Danlos syndrome, cutis laxa, renal failure and amyloidosis may hasten the development of dermatochalasis. In addition, some patients may have a genetic predisposition towards the development of dermatochalasis at a younger age.

In contrast, blepharochalasis stems from recurrent bouts of painless eyelid swelling, each instance of which may persist for several days. The swelling most likely represents a form of localized angioedema, although this remains speculative. Ultimately, after numerous episodes, the skin of the lids becomes thin and atrophic, and damage to the levator aponeurosis ensues. Blepharoptosis then develops (**Figure 87.25**). Blepharochalasis is idiopathic in most cases, though it has been linked to kidney agenesis, vertebral abnormalities and congenital heart defects in rare instances.

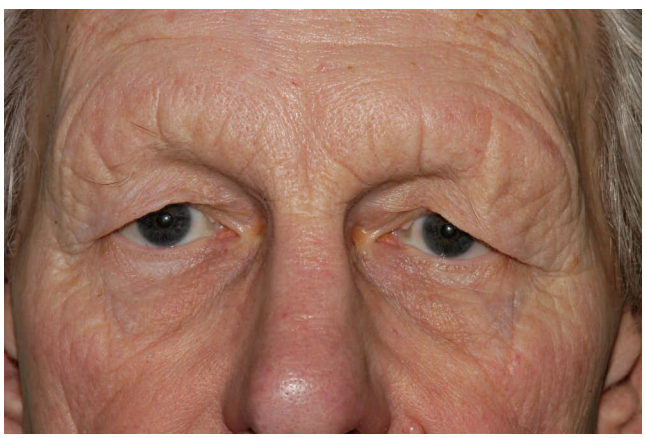


Figure 87.24 A female patient demonstrating bilateral brow ptosis and bilateral upper eyelid dermatochalasis.

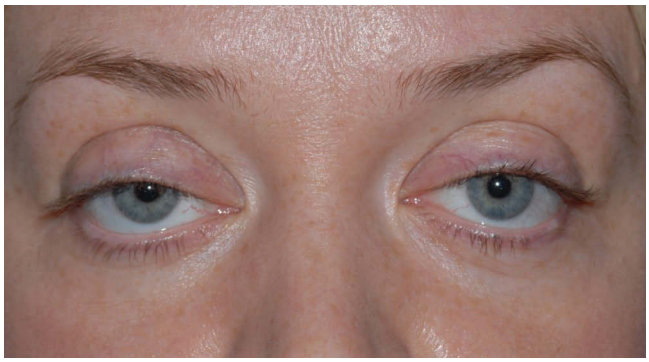


Figure 87.25 A young female patient with blepharochalasis showing bilateral blepharoptosis with raised skin creases, thinning of the upper eyelid skin and atrophy of the preaponeurotic fat pads. She also demonstrates a bilateral pseudoproptosis from high axial myopia.

UPPER EYELID BLEPHAROPLASTY

The goals of an upper eyelid blepharoplasty are:

- to remove an appropriate amount of excess upper eyelid skin alone, or skin and orbicularis muscle, in order to achieve the best cosmetic and functional result for the patient
- to remove or sculpt herniated orbital fat only where appropriate
- to create a symmetrical upper lid skin crease at an appropriate height for the individual patient
- to avoid visible scarring
- to avoid a secondary lagophthalmos or an incomplete blink
- to avoid exacerbating an associated brow ptosis.

An additional goal in the oriental patient is to create a visible upper eyelid crease.

Pre-operative patient evaluation

HISTORY

A careful history should be obtained. The patient's complaints, goals and expectations should be determined. The patient may be concerned about:

- an overhang of excess upper eyelid skin causing a loss of the superior visual field
- excess upper lid skin causing cosmetic problems
- upper lid fat herniation

- upper lid 'fullness'
- 'hooding' of the upper eyelids
- 'drooping eyelids'
- headaches from frontalis muscle fatigue
- a tired appearance commented on by friends or relatives.

The complaint of droopy upper eyelids may simply be due to severe dermatochalasis causing a pseudoptosis with the underlying eyelid height being normal. The lid position should be carefully evaluated, however, as a true blepharoptosis may also be present. If a true blepharoptosis is present, the patient must be carefully evaluated to diagnose the underlying cause of the blepharoptosis, such as an aponeurotic dehiscence from contact lens wear, Horner syndrome, myasthenia gravis or chronic progressive external ophthalmoplegia. Similarly, a severe dermatochalasis, often combined with a brow ptosis, may obstruct the patient's superior visual field.

Patients who have a moderate to severe brow ptosis and dermatochalasis are obliged to use their frontalis muscle to overcome the superior visual field defect. Such patients commonly develop deep forehead furrows (**Figure 87.26**). This leads to fatigue of the frontalis muscle, which in turn can cause a headache.

Occasionally, upper eyelid dermatochalasis and a lateral brow ptosis can lead to a secondary mechanical misdirection of eyelashes causing chronic ocular discomfort.

The cosmetic effects of upper eyelid dermatochalasis and brow ptosis can lead to complaints of a tired appearance. Lower eyelid fat herniation can also lead to similar complaints (see **Figure 87.1b**).

Patients should be specifically questioned about previous eyelid surgery. Patients who have previously undergone a cosmetic blepharoplasty or a facelift may omit such information, particularly if accompanied by a new partner. A history of contact lens wear, dry eye, facial palsy or thyroid dysfunction identifies a patient at risk of exposure keratopathy symptoms following an upper lid blepharoplasty.

It is important to exclude a bleeding disorder, as a post-operative haemorrhage following a blepharoplasty can be potentially sight-threatening. The use of aspirin or non-steroidal anti-inflammatory agents should be discontinued 2 weeks pre-operatively if the patient's medical status permits this. Any other non-prescription medications or dietary supplements that may predispose to excessive bleeding should also be discontinued (e.g. vitamin E supplements).

Any allergies should be carefully noted.

EXAMINATION

The patient should undergo a complete ophthalmic examination.

- The patient's best corrected visual acuity should be recorded.
- The palpebral fissures should be measured and the position of the skin creases documented after lifting the upper lid excess skin.
- The height and curvature of the upper eyelids relative to the pupils should be noted, and the MRD-1 and MRD-2 should be measured and recorded, looking for any evidence of true blepharoptosis.

  (The marginal reflex distance-1 (MRD-1) is the distance between the centre of the pupillary light reflex and the upper eyelid margin with the eye in primary gaze. A measurement of 4–5 mm is considered normal. The marginal reflex distance-2 (MRD-2) is the distance between the center of the pupillary light reflex and the lower eyelid margin with the eye in primary gaze.)
- The amount of pretarsal skin 'show' should be measured and recorded along with the amount of skin present from the lash line to the lowermost portion of the eyebrow, medially, centrally and laterally. This can be difficult in patients who pluck or tattoo their eyebrows (**Figure 87.27**).
- Any asymmetries should be noted. (It is important to make the patient aware of any pre-operative asymmetries,

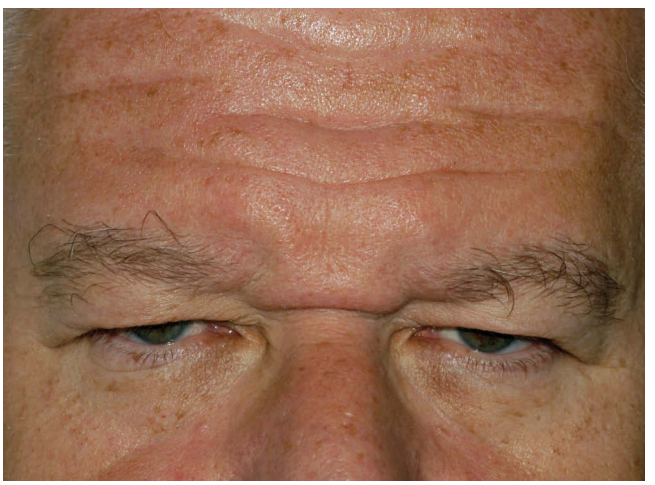


Figure 87.26 A patient with a severe bilateral brow ptosis and dermatochalasis causing visual field problems and headaches from frontalis overaction.

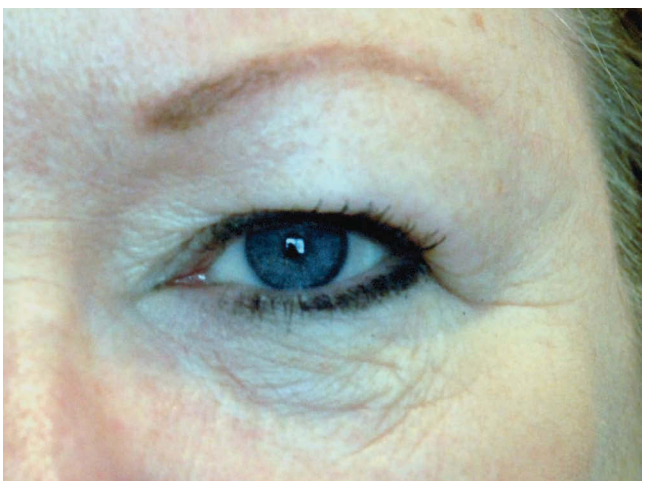


Figure 87.27 A patient with a plucked and tattooed eyebrow camouflaging the effects of a brow ptosis and a descent of the 'ROOF'.

which they may not have noticed. The patient will certainly notice asymmetries post-operatively!) Any frontalis overaction should be noted, and the position and shape of the brows observed after asking the patient to relax the frontalis muscle as much as possible. The secondary effects of brow ptosis on the upper eyelids must be recognized (see **Figure 87.24**).

- An assessment of the tear meniscus should be made using a slit lamp, and the tear film break-up time after the instillation of a drop of fluorescein should be documented.
- The upper lids should be everted to exclude the presence of any subtarsal lesions (e.g. papillae seen in atopy or with contact lens wear).
- The presence or absence of a Bell's phenomenon should be recorded.
- The degree of upper eyelid laxity is assessed to ensure that a 'floppy eyelid syndrome' is not overlooked. This is done by pulling downwards on the eyelid after grasping the eyelid margin and the eyelashes in the lateral aspect of the eyelid. Excessive eyelid laxity is also evident if eversion of the upper eyelid is very easy to perform.
- Any herniation of the medial and central preaponeurotic fat pads is noted in the upper eyelids, and of the medial, central and lateral preaponeurotic fat pads in the lower eyelids.
- The degree of excess upper eyelid skin is assessed and measured.
- The degree of any associated brow ptosis is noted along with any asymmetry. Any overaction of the eyebrow depressor muscles is also determined by noting the extent of glabellar frown lines and lateral canthal rhytids.
- The skin quality and degree of actinic damage is assessed. Specific dermatological disorders should be excluded (e.g. atopic dermatitis).
- The ocular motility should be assessed and recorded along with cover and alternate cover tests to exclude any horizontal or vertical ocular muscle imbalance.
- Any proptosis or pseudoproptosis due to axial myopia is noted. It may be much more difficult to achieve the desired surgical goals in such patients.
- The patient should be examined specifically to exclude the possibility of thyroid eye disease.

Pre-operative photographs must be taken. Pre-operative photographs are essential for patients who are to undergo any facial plastic and reconstructive surgery. They serve a number of useful purposes:

- a learning and teaching aid for the surgeon
- verification of the patient's disorder for healthcare insurance companies
- an aid to defence in a medicolegal claim
- to jolt the memory of the forgetful patient about their pre-operative appearance.

Written patient consent should be obtained before the photographs are taken. It should be made clear to the patient how the photographs are to be used.

The limitations of an upper eyelid blepharoplasty performed alone in the presence of significant brow ptosis should be explained. In these circumstances, an upper eyelid blepharoplasty should be very conservative in order to prevent further lowering of the brow and an unsatisfactory appearance. The patient should be carefully questioned to ascertain their expectations of surgery. Some patients with a mild degree of brow ptosis and upper lid dermatochalasis are better managed with the use of botulinum toxin injections, which, if used correctly, can create a satisfactory and pleasing brow lift. The injection can be given into the lateral rhytids and tail of the eyebrow (30–60 units of Dysport® per side given as four or five separate intramuscular injections), and can be combined with injections into the glabella (80–120 units of Dysport® given as four to six separate intramuscular injections) paralyzing the brow depressors and allowing the frontalis muscle to act unopposed. If an unwanted temporal peaking of the brows occurs, 5–10 units of botulinum toxin can be injected 1–2 cm above the lateral brow into the overacting frontalis.

If botulinum toxin injections are to be used as a trial prior to surgery, this should be undertaken 2 weeks beforehand. The injections should not be given at the time of surgery as post-operative oedema will cause the toxin to spread to other muscles (e.g. to the levator muscles), causing a blepharoptosis.

Where a brow ptosis is significant, it is far preferable to address this by one of a number of surgical approaches, depending on the degree of brow ptosis and the age and preferences of the patient. The options for a brow lift procedure include:

- direct brow lift
- 'gull wing' direct brow lift
- temporal direct brow lift
- internal suture browpexy
- transblepharoplasty Endotine implant brow lift
- mid-forehead brow lift
- subcutaneous forehead and brow lift
- pretrichial brow lift
- coronal brow lift
- endoscopic brow lift
- brow lift using dissolvable 'coned' suture devices.

Figure 87.28a illustrates the problem posed by a female patient requesting an upper eyelid blepharoplasty who demonstrates a bilateral brow ptosis. A blepharoplasty alone would be inappropriate. **Figure 87.28b** demonstrates her post-operative appearance 4 months following a bilateral upper eyelid skin/muscle blepharoplasty combined with a bilateral endoscopic brow lift.

INFORMED CONSENT

The advantages, disadvantages, risks and potential complications of the procedure should be discussed with the patient in great detail. The siting of incisions and anticipated scars should be explained. The risks and the incidence of complications need to be outlined in an open and

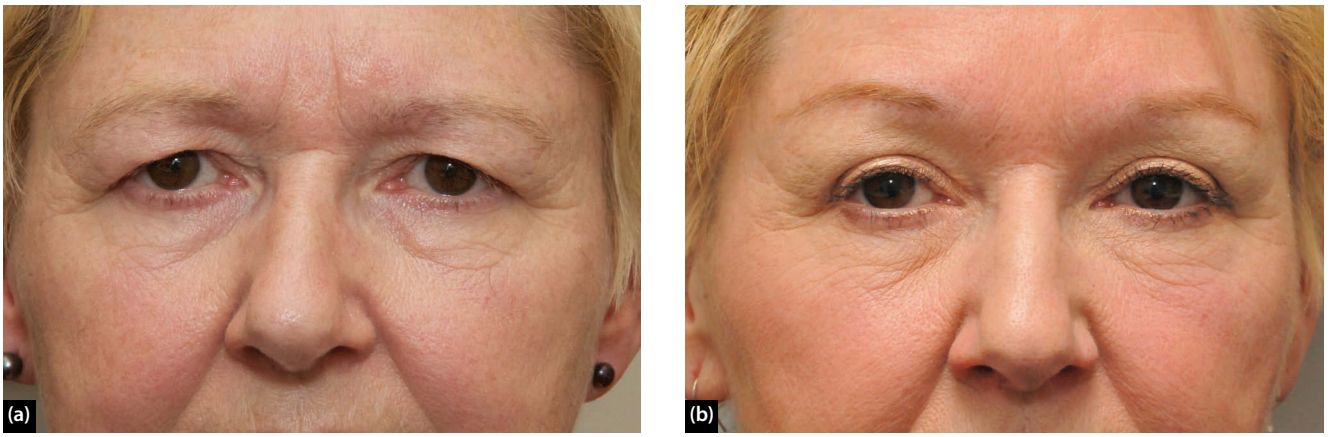


Figure 87.28 (a) A female patient with bilateral brow ptosis and upper eyelid dermatochalasis. **(b)** The same patient 4 months following a bilateral endoscopic browlift and upper lid blepharoplasty.

honest manner. The consequences of complications and their management should also be outlined. The patient should also be provided with a formal document which outlines the potential complications of blepharoplasty surgery, their management and the financial responsibilities that would be incurred.

The description of any blepharoplasty procedure as 'basic', 'straightforward', 'simple', 'minor' or 'routine' should be avoided.

Many patients seeking cosmetic blepharoplasty request that their general practitioner is not informed. A detailed letter outlining the patient's complaints, the clinical findings, the management options which have been discussed, the risks and potential complications of surgery, advice about the discontinuation of aspirin or anti-inflammatory drugs, the anticipated recovery period and aftercare instructions should, however, be sent to the patient and retained in their clinical records. The patient should be encouraged to give further consideration to the options discussed before making a decision to proceed with surgery. This also avoids any misunderstandings on the part of the patient. It may necessitate a further consultation or an attendance at a pre-assessment clinic to obtain fully informed consent and to answer any residual queries. The patient should not be asked to sign a consent form for an elective cosmetic procedure on the day of surgery.

Surgical technique

MARKING THE UPPER EYELID

Marking the upper eyelid skin crease with the patient sitting upright, before the injection of any local anaesthetic solution, is the first very important step in a successful upper eyelid blepharoplasty. A drop of proxymetacaine is instilled into each eye. The upper eyelid skin is cleaned with an alcohol wipe, and the skin crease marked with a cocktail stick that has been dipped into a gentian violet marker block. A calliper should be used to measure the height of the crease. The fellow eyelid should be marked simultaneously, ensuring precise symmetry. The skin crease should be marked at a lower level in a male patient.

Figure 87.29 Marking the eyelid. The skin just above the skin crease marking is gently pinched with toothed forceps to ensure that passive closure of the eye is not compromised. This is repeated medially and laterally and the proposed skin excision is marked.

The skin above the crease centrally is gently pinched with a pair of fine-toothed forceps. Great care should be taken to ensure that the eyelids can close passively. Any temptation to remove more than 8–10 mm of skin should be resisted, particularly in the presence of an uncorrected brow ptosis. The superior aspect of the pinched skin is marked and an ellipse is drawn (**Figure 87.29**).

The relative dimensions of this area divided into thirds should be remembered to maintain a good aesthetic appearance. (The distance between the inferior aspect of the eyebrow and the upper lid skin crease on downgaze should be approximately two-thirds of the distance from the inferior aspect of the eyebrow to the eyelid margin. Likewise, the distance from the skin crease to the eyelid margin in downgaze should be one-third of the distance from the inferior aspect of the eyebrow to the eyelid margin.) In general, at least 10–12 mm of skin should be left between the inferior aspect of the eyebrow and the superior skin excision marking (**Figure 87.30**). It is important

not to carry the incision markings into the medial canthal area to avoid webbed scars.

If there is no temporal hooding of skin, the lateral aspect of the incision should be kept within the orbital margin (**Figure 87.30**). If there is temporal hooding, a lateral wing can be added to the crescent leaving the resulting scar running in a horizontal direction (**Figure 87.31**). The patient should be warned that this lateral scar will be visible and will not be hidden with the upper lid skin crease.

ANAESTHESIA

The procedure may be undertaken under general anaesthesia, local anaesthesia or local anaesthesia with intravenous sedation. Local anaesthesia, preferably with carefully titrated intravenous sedation provided by an anaesthetist, is advantageous as it allows voluntary levator muscle function to be used to assist in the identification of eyelid structures. This is particularly important when an upper eyelid blepharoplasty is being performed in conjunction with a levator aponeurosis advancement procedure to correct blepharoptosis.

The patient should be kept in a semirecumbent position with the head elevated at least 30 degrees to reduce venous engorgement and bleeding. Normal saline sachets should be kept available in the refrigerator and used to moisten 4 × 4 gauze swabs, which are applied to the operated side while the fellow side is undergoing the same procedure.

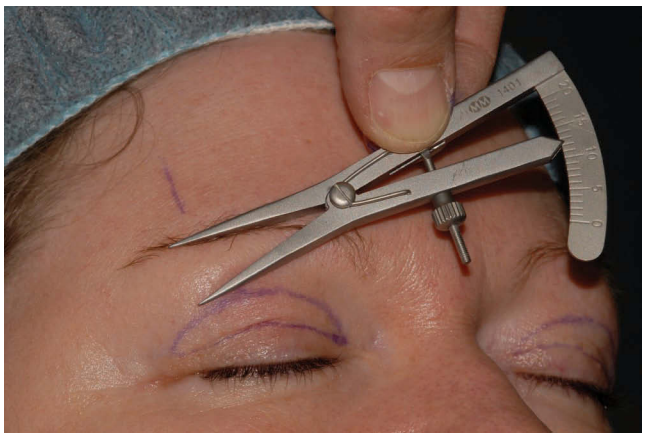


Figure 87.30 Eyebrow–superior skin excision mark distance. Here 12 mm of skin has been left between the inferior aspect of the eyebrow and the superior skin excision marking.

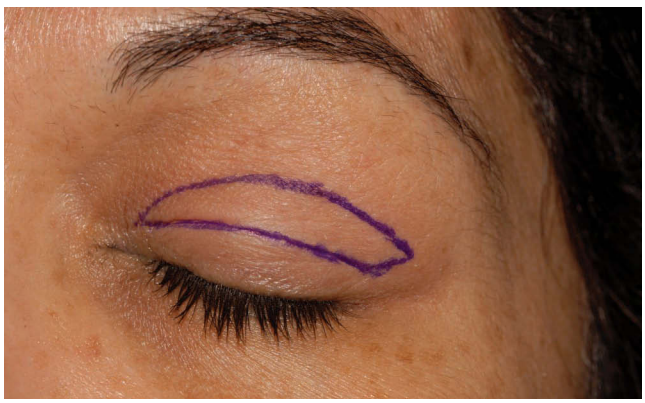


Figure 87.31 Final markings. The desired position of the upper eyelid skin crease has been marked with a cocktail stick dipped into a gentian marker block. The skin above the crease has been gently pinched while asking the patient to passively close the eye at the same time as an assistant gently raised the eyebrow with a finger. The markings are not taken medially beyond the limit of the skin crease. Laterally a small 'wing' has been added in this patient to prevent a 'dog ear'. A distance of 10–12 mm has been left between the inferior aspect of the brow and the superior aspect of the skin resection all along the length of the skin marking.

SURGICAL PROCEDURE

1. Approximately 2–3 mL of 0.5% marcain with 1:200 000 units of adrenaline mixed 50:50 with 2% lignocaine with 1:80 000 units of adrenaline are injected just beneath the skin with a single pass of the needle if possible, avoiding the underlying orbicularis oculi muscle in order to prevent the occurrence of a haematoma. The needle is inserted temporally and advanced nasally while slowly injecting the solution. Immediate pressure should be applied for a few minutes. A pause of 10 minutes is allowed for the adrenaline to take effect.
2. The patient is prepped and draped, ensuring that the drapes do not place any downward pressure on the eyebrows.
3. A 4.0 silk traction suture is inserted along the grey line of the upper eyelid and fixated to the face drapes with a curved artery clip, providing downward traction on the eyelid. This makes the skin incision easier to undertake and provides protection for the eye.
4. The skin incision is made along the gentian violet markings with a Colorado needle.
5. A skin flap is developed and dissected off the underlying orbicularis oculi muscle (**Figure 87.32**). A strip of orbicularis muscle can then be dissected off the underlying orbital septum. If the patient merely requires the removal of excess skin, and any orbicularis muscle for functional reasons, the skin can be closed with simple interrupted 7-0 Vicryl sutures. This surgical procedure is quick and relatively simple to perform and does not expose the patient to the small risks of a postoperative intraorbital haemorrhage.

   In patients who are at an increased risk of exposure keratopathy, a simple skin excision alone can be performed, preserving the underlying orbicularis muscle. In some patients, however, this can result in some bunching of the orbicularis muscle with a less satisfactory aesthetic result. Alternatively, a central 3–5 mm strip of orbicularis muscle can be removed.
6. If the patient requires the removal, sculpting or redraping of orbital fat, the orbital septum is opened along its entire length.
7. The central preaponeurotic fat is allowed to prolapse. This can be sculpted with the Colorado needle using the coagulation mode and any larger vessels cauterized with bipolar cautery. The fascial septa around

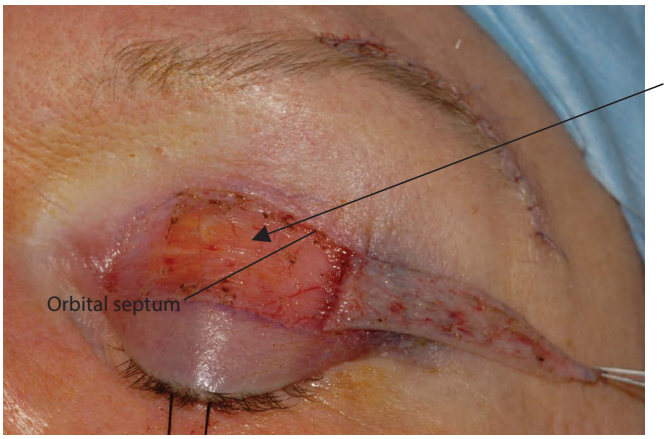


Figure 87.32 A skin flap has been created, exposing the underlying orbicularis oculi muscle. This patient has also undergone a temporal direct brow lift.

and within the medial fat pad can be gently opened and separated using the Colorado needle.

8. If fat needs to be removed, the fat should be carefully clamped using a small curved artery clip. The artery clip should be held carefully by the assistant. Great care should be taken to avoid anterior traction on the fat that can lead to rupture of posterior orbital vessels and a sight-threatening retrobulbar haematoma. The fat is removed using the Colorado needle on cautery mode. The artery clip should be released very slowly and carefully, and immediately reapplied if any vessels bleed. This is particularly important when removing fat medially. Great care should also be taken not to damage the medial horn of the levator muscle or the trochlea. It should be noted, however, that fat removal should be undertaken very conservatively, if at all, in the upper lid so as to avoid a secondary hollowing of the upper eyelid, which can result in a very aged appearance. The fat should be retained within a swab moistened with sterile saline as it may be divided into small fat pearls and used as a free graft in the opposite upper eyelid to address an asymmetry or in the lower eyelid to assist in the camouflage of a tear trough defect.
9. The skin is closed with interrupted 7-0 Vicryl sutures, taking bites of the very edges of the skin. The type of skin closure is determined by the type of skin crease that is required. If this is to be a soft, less well-defined crease, the skin can be closed as above. If a higher, well-defined crease is required, usually in a female, the skin is closed with interrupted 7-0 Vicryl sutures that incorporate a bite of the underlying levator aponeurosis. It is sometimes advantageous to remove a strip of orbicularis muscle from the inferior skin wound edge but this can lead to bleeding, particularly if the effects of the adrenaline have begun to wear off.

POST-OPERATIVE CARE

Post-operatively the patient is prescribed a topical antibiotic ointment to be applied to the upper lid wounds three times a day for 2 weeks and Lacri-Lube® ointment 1–2 hourly to the eyes for 48 hours and at bedtime. The Lacri-Lube® ointment is then changed to preservative-free topical lubricant drops to be used hourly during the day and Lacri-Lube® is continued at bedtime until the degree of lagophthalmos has improved. The frequency of the lubricants is then gradually reduced over the course of the next few weeks. The patient is instructed to sleep with the head of the bed elevated for 4 weeks and to avoid lifting any heavy weights for 2 weeks. Clean cool packs are gently applied to the eyelids intermittently for 48 hours. The patient should be reviewed in clinic within 2 weeks and again within 4–6 weeks. The upper lid skin sutures are removed at 2 weeks.

LOWER EYELID BLEPHAROPLASTY

The goals of a lower eyelid blepharoplasty are:

- to remove an appropriate amount of excess lower eyelid skin and muscle if required
- to remove or reposition herniated fat where appropriate
- to avoid middle lamellar scarring and eyelid retraction
- to address any associated lower eyelid or lateral canthal tendon laxity
- to avoid any post-operative ectropion and secondary epiphora.

An emerging concept in cosmetic surgery holds that the face develops the characteristics of ageing as a result of not only elastosis and sagging but also soft-tissue atrophy. The evolution of this concept is well illustrated in the field of lower lid blepharoplasty, in which the traditional approach to the surgical improvement of lower eyelid 'bags' has been to resect the herniating preaponeurotic fat. While this method can indeed remove 'bags', in many patients it may also eliminate the soft tissue that conceals the inferior orbital margins, creating a hollowed, skeletonized appearance. This is in contrast to the appearance of the youthful face, in which soft-tissue fullness creates a smooth transition from the cheek to the lower eyelid. The inferior bony orbital margin is concealed. The traditional approach of resecting orbital fat is therefore unlikely to produce a full, youthful lower lid contour and conflicts with the concept that facial ageing is partly a consequence of soft-tissue atrophy.

A number of alternative surgical approaches have been devised to address this problem. One such technique that has gained prominence is the arcus marginalis release, in which preaponeurotic fat is advanced and repositioned rather than resected, in order to reconstruct the soft tissue of the lower eyelids. This technique is designed to conceal the underlying bony structure of the inferior orbit in an attempt to impart a more youthful contour to the periorbital area. Alternatively, a SOOF lift or a midface lift may be undertaken in conjunction with a lower eyelid blepharoplasty in order to achieve the same goals, but the patient then has to accept a more extensive surgical dissection and a longer period of recuperation with more post-operative bruising and swelling.

Pre-operative patient evaluation

HISTORY

The patient's complaints, goals and expectations should be determined. The patient may be concerned about:

- loose folds of skin
- lower eyelid 'bags'
- dark circles beneath the eyes
- skin wrinkles and/or signs of photodamage
- malar mounds
- lower eyelid 'festoons'.

EXAMINATION

As for an upper eyelid blepharoplasty, the patient should undergo a complete ophthalmic examination.

- The patient's best-corrected visual acuity should be recorded.
- The palpebral fissures should be measured and the position of the lower eyelid with respect to the inferior limbus noted. The MRD-1 and MRD-2 should be measured and recorded.
- Any asymmetries or scleral show should be noted.
- The patient's lower lid appearance at rest and on smiling should be compared.
- The relationship of the globe to the inferior orbital margin should be noted, particularly the degree to which the globe protrudes beyond the inferior orbital margin in profile view. A globe which protrudes beyond the inferior orbital margin is referred to as a 'negative vector' configuration. Such patients are more at risk of post-operative problems with eyelid retraction and scleral show following a lower eyelid transcutaneous blepharoplasty.
- An assessment of tear production and the tear film should be undertaken using a slit lamp and the findings documented.
- Any 'herniation' of the lower eyelid fat pads is noted and their positions documented. The skin quality and degree of actinic damage is assessed.
- The degree of lower eyelid laxity is assessed. This can be quite subjective but, as a general rule, if the lower eyelid can be distracted from the globe by more than 6–8 mm or if the eyelid does not return to its position after release without a blink (a positive 'snap test'), the eyelid can be considered to have sufficient laxity to warrant a lower eyelid tightening procedure.
- Any proptosis or pseudoproptosis due to a large globe is noted. It may be more difficult to achieve the surgical goals in such a patient. The patient should be examined specifically to exclude the possibility of thyroid eye disease.
- The appearance of the infraorbital margin is carefully assessed. Almost any patient seeking a lower eyelid blepharoplasty with lower eyelid 'bags' and/or a skeletonization of the inferior orbital margin is a candidate for an arcus marginalis release. In contrast, however, younger patients with a congenital excess of orbital fat are less likely to benefit from this technique. These patients are better managed using a traditional resection of the excess fat via a transconjunctival approach, with the use of CO_2 skin resurfacing or a chemical peel to manage any associated lower eyelid skin wrinkling and photodamage.

Just as the upper lid cannot be properly assessed without also taking into consideration the position of the eyebrow, the lower lid should not be examined in isolation but account should be taken of any associated midface ptosis and midface fat atrophy. Such a patient may require a SOOF lift, or a midface lift and/or volume augmentation of the cheek and tear trough using dermal fillers or structural fat grafting.

INFORMED CONSENT

The guidelines for consent are as detailed in 'Upper eyelid blepharoplasty' above.

Surgical approaches

A lower eyelid blepharoplasty procedure should ideally be tailored to the individual requirements of a patient. The surgical approach selected depends on a pre-operative assessment of fat 'herniation', the degree of skeletonization of the inferior orbital margin, the presence of a lower lid double convexity, the amount of excess lower eyelid skin, the degree of static wrinkling and actinic damage, the degree of orbicularis oculi muscle ptosis, the presence and degree of midface ptosis and midface fat atrophy, the presence of 'malar mounds' or festoons, and the degree of lower eyelid or lateral canthal tendon laxity. The procedure may be performed in conjunction with another surgical procedure (e.g. an orbital decompression procedure in thyroid eye disease).

The patient should be carefully evaluated to determine whether alternative non-surgical treatments might be better suited to their needs. This will depend on the patient's individual circumstances and age. Some patients with the complaint of lateral canthal rhytids ('laughter lines') and lateral eyelid skin wrinkling alone may be better managed with botulinum toxin injections. These can be given into the lateral rhytids (30–60 units of Dysport® per side given

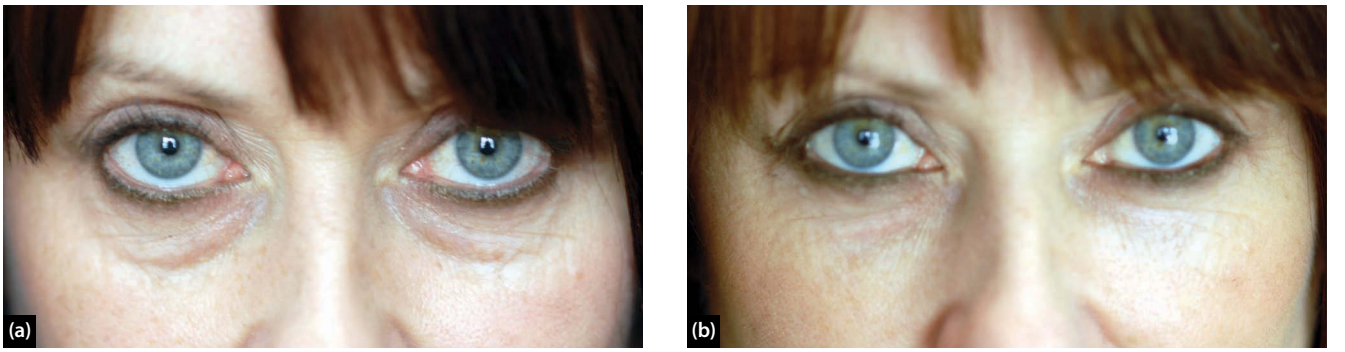


Figure 87.33 (a) Bilateral lower eyelid 'tear tough' defects. **(b)** The appearance of the same patient 2 weeks following the injection of a hyaluronic acid filler (Restylane®) along the inferior orbital margins.

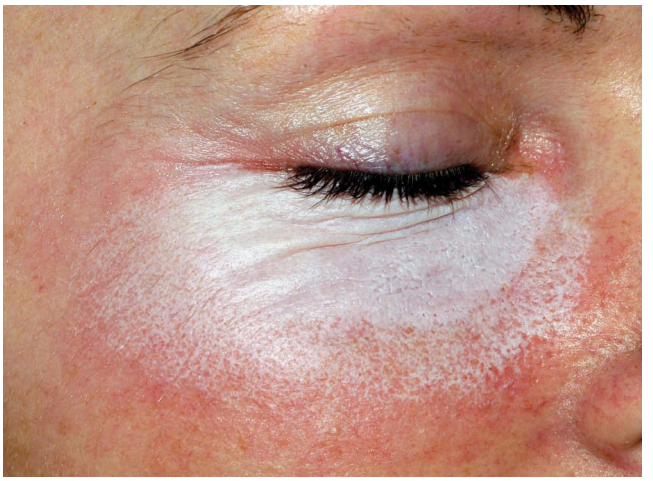


Figure 87.34 A lower eyelid 35% Jessner's/TCA peel.

as four or five injections) with the addition of tiny amounts to the lateral lower lid orbicularis muscle (two or three injections of 2–3 units of Dysport®). Injections should not be given in the medial aspect of the lower eyelid, as this is associated with the risk of spread to involve the inferior oblique muscle. In addition, higher doses should be avoided in the lower eyelid to avoid undue weakness to the orbital portion of the orbicularis muscle with the risk of the patient developing a malar 'bag'.

Hyaluronic acid filler injections (e.g. Restylane® or Juvéderm®) can be used to camouflage the tear toughs in suitable candidates (see **Figure 87.28**). Alternatively, a Jessner's/trichloroacetic acid peel (TCA) or CO_2 laser resurfacing can be considered to treat age- and solar-related skin wrinkling in the lower eyelids (**Figures 87.33** and **87.34**).

For patients who are better suited to surgical management there are two main surgical approaches:

- transcutaneous lower lid blepharoplasty
- transconjunctival lower lid blepharoplasty.

These procedures can be supplemented by other techniques to enhance the result:

- horizontal eyelid tightening procedure
- 'pinch' technique skin resection (in the case of a transconjunctival lower lid blepharoplasty)
- CO_2 laser resurfacing
- Jessner's/TCA peel
- botulinum toxin injections
- injection of dermal fillers or autogenous fat to provide soft tissue enhancement
- SOOF lift
- midface lift
- placement of a cheek implant.

A transconjunctival approach is preferred for patients with 'fat herniation' but no significant skin excess. This approach avoids an external scar and is also ideal for patients who have previously undergone a transcutaneous blepharoplasty but who require revision surgery for residual 'fat herniation'. It can be combined with CO_2 laser resurfacing or with a Jessner's/TCA peel to deal with skin wrinkling in those patients who are prepared to cooperate with the more onerous post-operative care and the avoidance of sun exposure (**Figure 87.35**).

Surgical technique

A lower eyelid blepharoplasty can be performed under general anaesthesia, local anaesthesia or local anaesthesia with intravenous sedation. Local anaesthesia affords the surgeon the opportunity of asking the patient to look up and to open the mouth to avoid excessive skin resection during a transcutaneous blepharoplasty. The patient should be draped using non-adhesive drapes to allow free movement of the lower eyelid and cheek. The upper lid skin crease may need to be marked or, if the procedure is to be combined with an upper lid blepharoplasty, the upper lid skin excision should be marked as described above.

TRANSCUTANEOUS BLEPHAROPLASTY WITH ARCUS MARGINALIS RELEASE, FAT REPOSITIONING AND ORBICULARIS OCULI MUSCLE SUSPENSION

The patient is advised pre-operatively that the lateral aspect of the lower eyelids will be unnaturally high for the first 2–3 weeks following this procedure. As the absorbable 5–0 Vicryl suture holding the orbicularis muscle flap in place begins to give way, the lateral aspect of each lower eyelid gradually assumes its normal position.

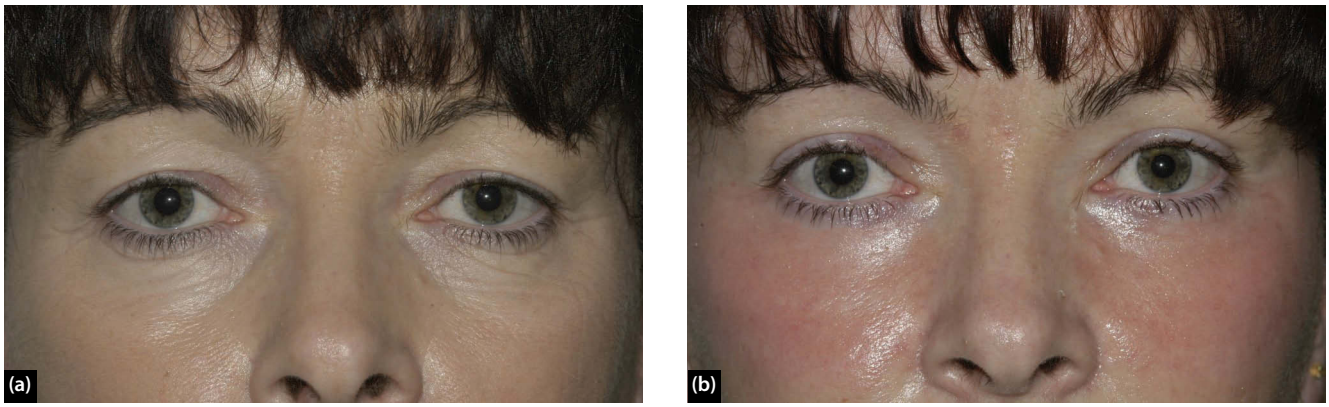


Figure 87.35 (a) The pre-operative appearance of a patient with moderate lower eyelid rhytids. **(b)** The post-operative appearance of the same patient 2 weeks following a bilateral upper eyelid blepharoplasty and lower eyelid CO_2 resurfacing (prior to the application of camouflage mineral make-up) demonstrating improvement in skin wrinkling but with typical post laser erythema.

Surgical procedure

1. Approximately 2–3 mL of 0.5% marcain with 1:200 000 units of adrenaline mixed 50:50 with 2% lignocaine with 1:80 000 units of adrenaline are injected with aouipl single injection just beneath the skin along the lower eyelid just below the tarsus and a further 2 mL is injected along the upper lid skin crease. The needle is inserted temporally and advanced nasally while slowly injecting the solution. Immediate pressure is applied. A pause of 10 minutes is allowed for the adrenaline to take effect.
2. The patient is prepped and draped.
3. A 4-0 silk traction suture is placed through the grey line of the lower eyelid and fixated to the head drape with a curved artery clip. A subciliary incision is made with a Colorado needle 1.5 mm below the eyelid margin to avoid damaging the eyelash follicles. This is commenced just beneath the inferior punctum and extends to the lateral canthus where it is continued within a lateral rhytid for a few millimetres (**Figures 87.36** and **87.37**). The dissection plane first passes subcutaneously for a few millimetres until the inferior margin of the tarsus is reached, at which point the dissection plane passes deep to the orbicularis oculi muscle (**Figure 87.37**). In this way, the pretarsal orbicularis oculi muscle is preserved, thereby minimizing the risk of denervation and, consequently, a paralytic eyelid ectropion.
4. A skin–muscle flap is dissected from the underlying orbital septum down to the inferior orbital margin.
5. Now exposed, the arcus marginalis is incised using the Colorado needle from a medial to lateral direction along the infraorbital rim, taking care to avoid the inferior oblique muscle and the lateral canthal tendon (**Figure 87.37**).
6. The septum and released preaponeurotic fat are then advanced over the inferior orbital margin. If necessary, the lateral fat pad may be trimmed as it may not be possible to reposition this adequately. It is very important to avoid undue traction on the fat pads in order to avoid tearing deep orbital veins which can in turn lead to a sight-threatening retrobulbar haemorrhage. The fat should not be discarded, however, as it can be placed over the inferior orbital margin and used to further recontour the nasojugal groove and the lateral tear tough. Likewise, fat removed during the course of a simultaneous upper lid blepharoplasty should not be discarded. Any fat removed should be kept in a swab moistened with saline and reimplanted without undue delay.
7. The fat pads may need to be sculpted to achieve a smooth contour. Meticulous technique is critical at this stage, since irregularities in the contour of the advanced fat pads are noticeable through the skin. The advanced septum and orbital fat are reset (as a unit) onto the periosteum of the maxilla inferior to the orbital rim with interrupted 5-0 Vicryl sutures (**Figures 87.38** and **87.39**).

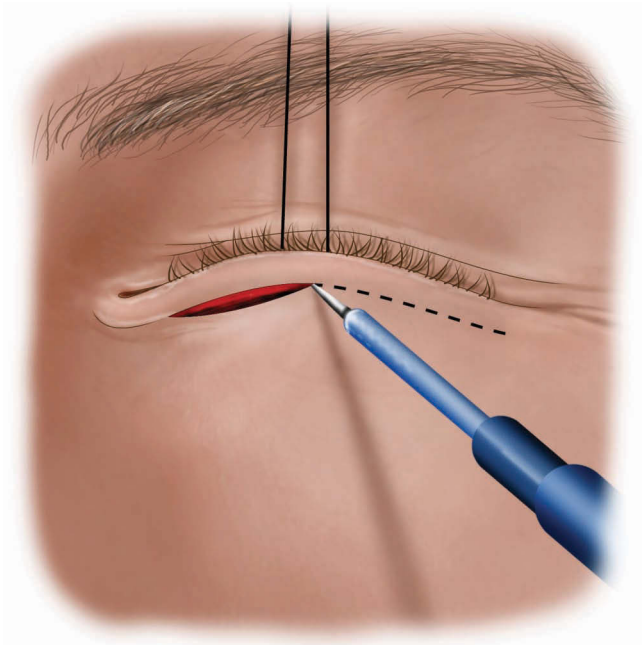


Figure 87.36 A subciliary incision is made with a Colorado needle with the lower eyelid placed on traction.

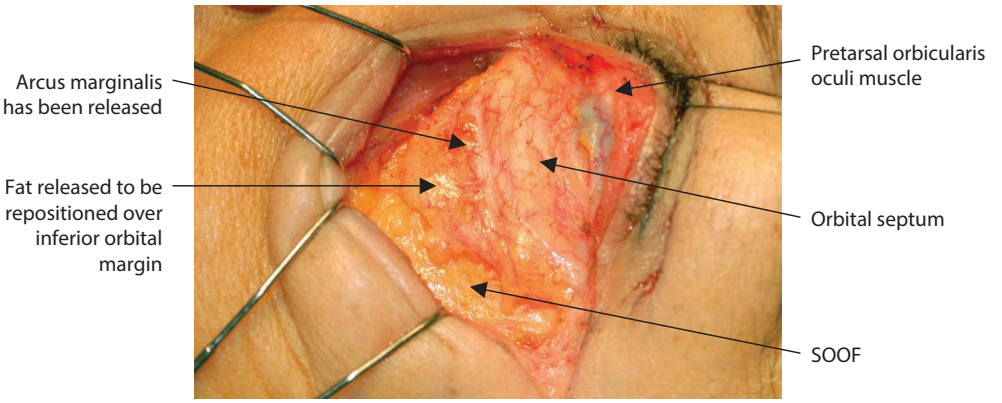


Figure 87.37 The anatomy of the left lower eyelid as seen during the course of a transcutaneous lower lid blepharoplasty.

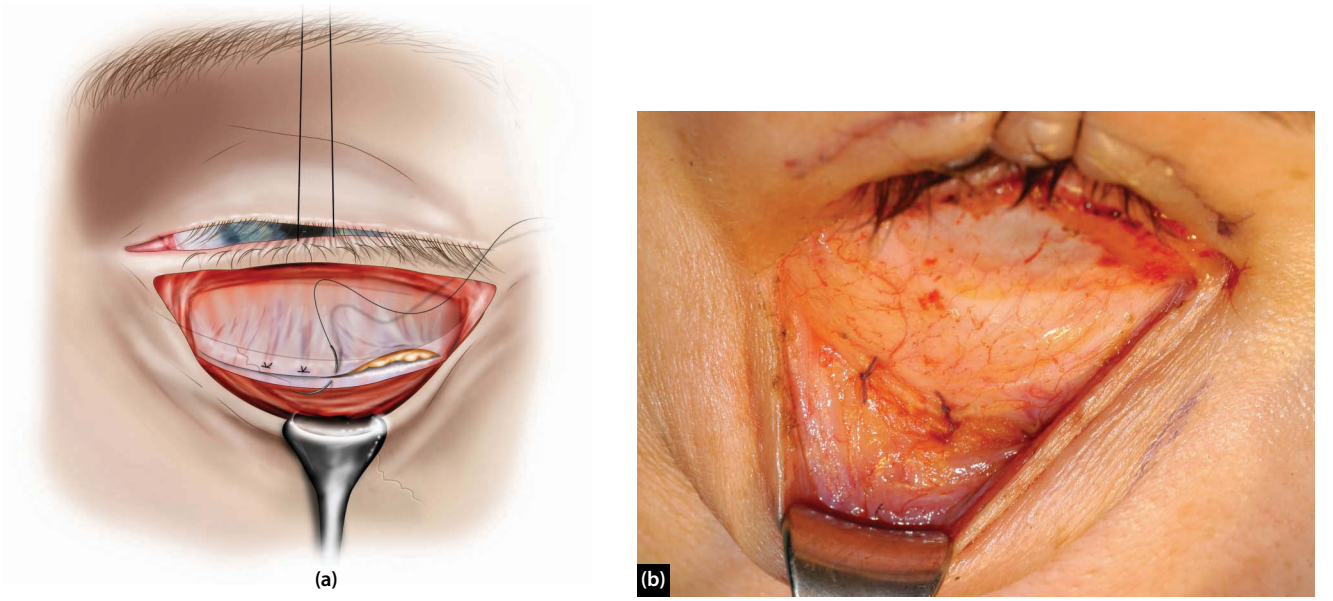


Figure 87.38 (a) Diagram showing the septum and fat being advanced over the inferior orbital margin and sutured to the periosteum just below the inferior orbital margin. **(b)** Intra-operative photograph of the septal reset procedure.

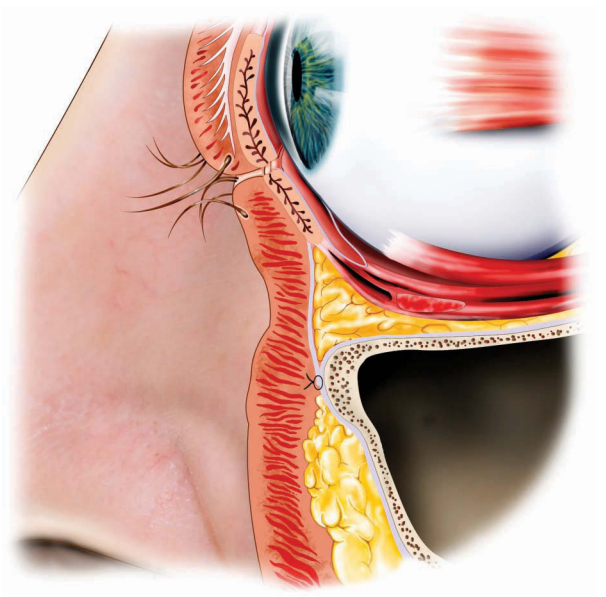


Figure 87.39 A more convex eyelid–cheek junction is created as the septal reset is performed and the orbicularis muscle is moved superolaterally.

8. The septum should be reset under minimal tension to avoid scleral show or an ectropion. If resetting the septum results in any eyelid retraction, the fat alone can be repositioned and sutured.
9. A lateral upper lid skin incision is made using the Colorado needle. The dissection is carried down through the orbicularis muscle to the orbital septum. This is then traced to the lateral orbital margin where the periosteum is exposed.
10. Stevens scissors are then used to bluntly dissect beneath the lateral orbicularis oculi muscle creating a tunnel (**Figure 87.40**).
11. A lateral tightening procedure may be required depending on the degree of lower lid laxity and should be performed before the septum is repositioned in order to establish and stabilize the position of the eyelid (**Figure 87.41**). (This is in fact very rarely required in patients under the age of 60 years.) Using a 15 blade, a tiny incision is made at the lateral commissure. A double-armed 5-0 Prolene suture on a round-bodied needle is passed through the incision, emerging through the lateral upper lid incision.

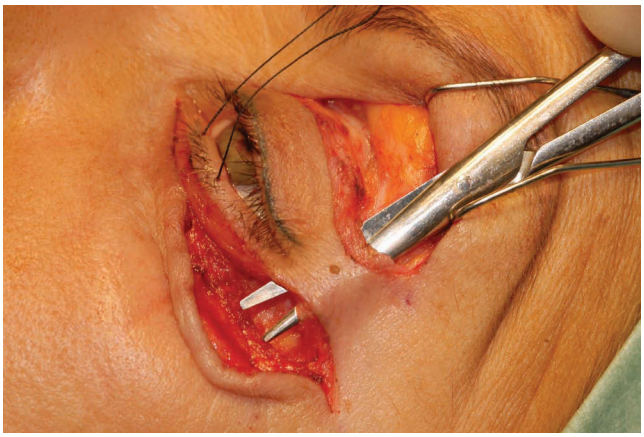
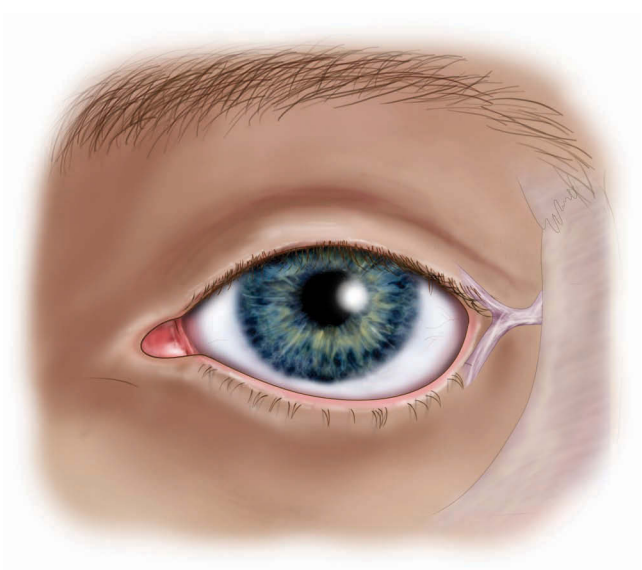
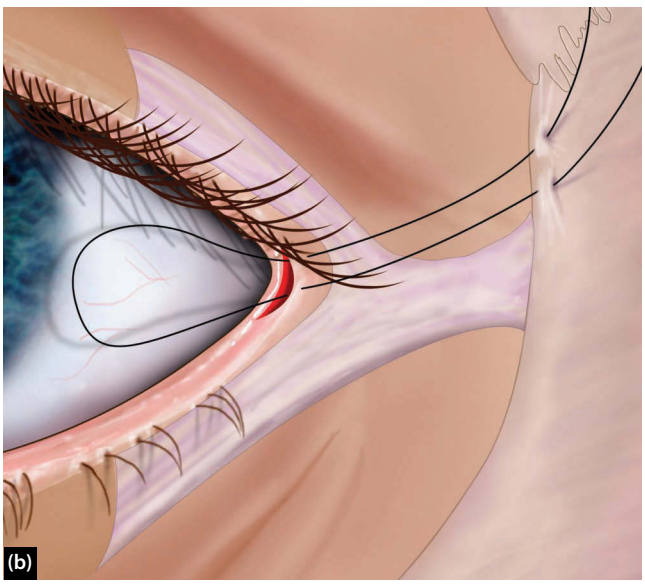
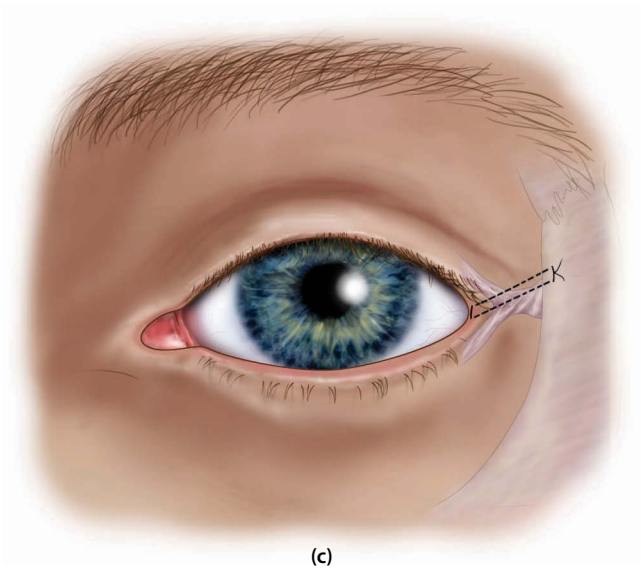


Figure 87.40 Stevens scissors are used to create a tunnel under the lateral orbicularis oculi muscle. In this patient, the lower eyelid blepharoplasty is being combined with an upper eyelid blepharoplasty.







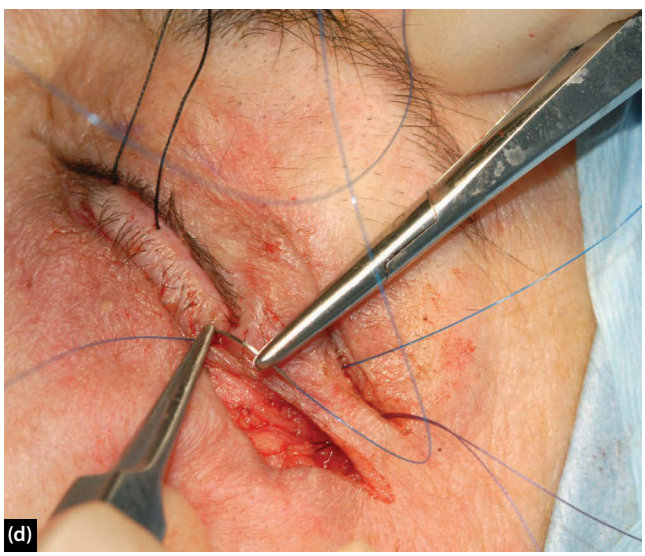


Figure 87.41 (a) Laxity of the lower eyelid with inferior scleral 'show'. **(b, c)** A lateral canthal tightening suture. The lateral canthal tendon and the lateral orbital margin are exposed via a lateral upper lid skin crease incision. **(d)** An intra-operative photograph showing the placement of the Prolene suture through a small incision at the lateral commissure. *(Continued)*

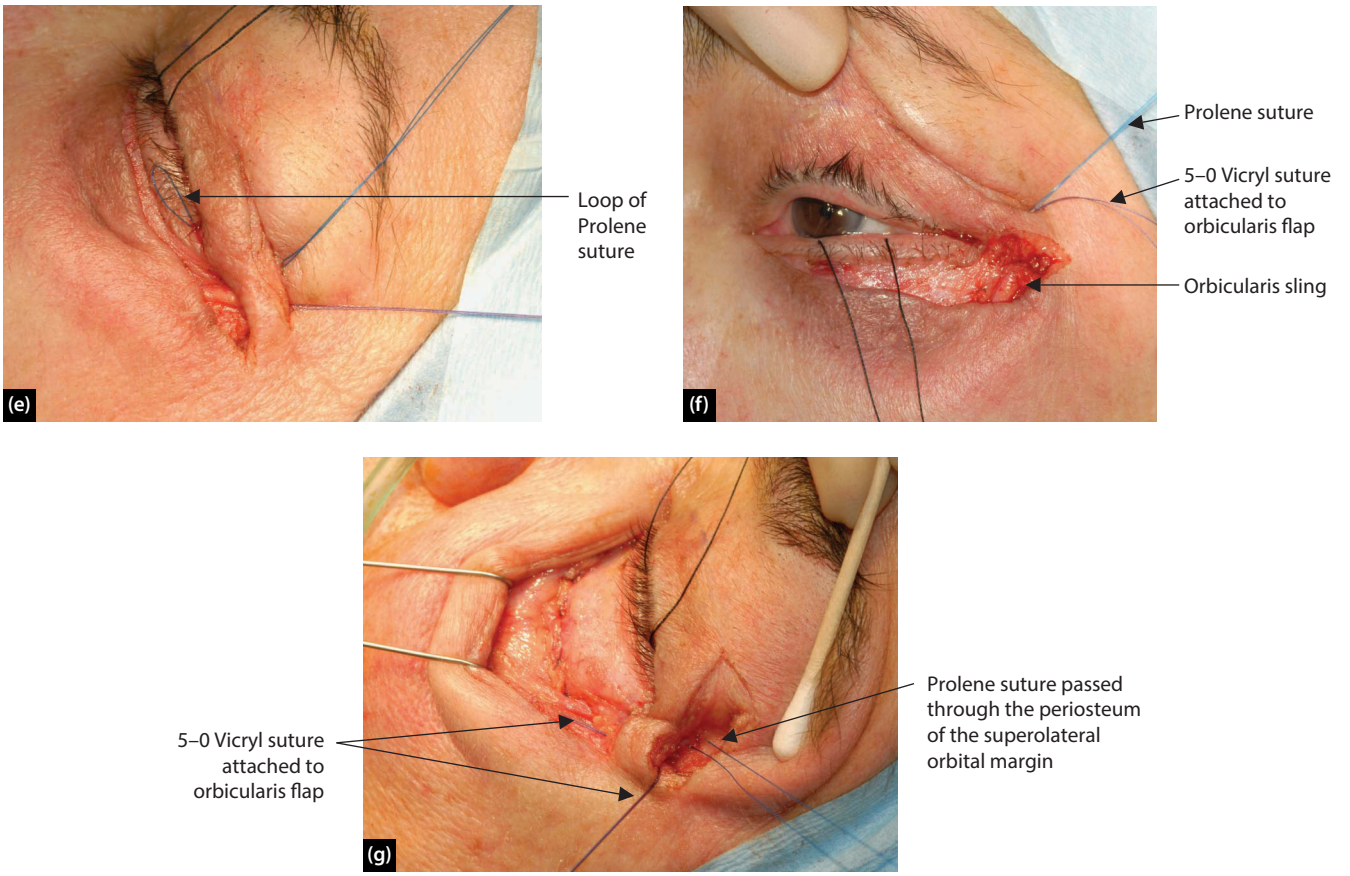


Figure 87.41 (Continued) **(e)** The loop of the Prolene suture is seen between the upper and lower eyelids laterally before the suture is tightened. **(f)** The Prolene suture has been tightened. The lower eyelid contour and height are checked to ensure that these are satisfactory. **(g)** The placement of the Prolene suture through the periosteum of the superolateral orbital margin is demonstrated.

Each needle is then passed through the periosteum of the internal aspect of lateral orbital wall in a medial to lateral direction and tied on the external surface of the lateral orbital wall, burying the knot (see **Figure 87.35**). Greater degrees of laxity of the lower eyelid and lateral canthal tendon should be addressed using a lateral tarsal strip procedure.

12. The orbicularis oculi muscle is now repositioned. With the use of this manoeuvre, lateral eyelid tightening is rarely if ever required in patients under the age of 60 years. From the dissection plane already created superficial to the septum and arcus marginalis, the lower lateral orbicularis is elevated off the underlying malar eminence with Westcott scissors, extending inferiorly in the submuscular plane as far as necessary to free the muscle's inferior border.
13. After separating the orbicularis oculi muscle from the skin of the lower lateral eyelid using Westcott scissors, a triangular muscle pedicle is created, with the base anchored inferolateral to the lateral canthus (**Figure 87.42**). Any redundant orbicularis muscle medial to the pedicle is removed with Westcott scissors.
14. A double-armed 5-0 Vicryl suture on a half circle needle is passed through the orbicularis flap and the suture is passed under the bridge of skin and orbicularis muscle at the lateral canthus.
15. The needles are passed through the periosteum of the superolateral orbital margin from medial to lateral and tied (**Figure 87.43**).
16. Moderate tension is maintained on the lower eyelid traction suture to prevent an over-resection of skin. If the surgery has been performed under local anaesthesia, the patient is asked to look up and to open the mouth to further assist in ensuring that an over-resection of skin is avoided. The skin is incised vertically at the lateral canthus using straight iris scissors. The redundant skin is then excised medial and lateral to the vertical incision using the same straight scissors (**Figure 87.44**). Care is taken to manage any residual dog ear at the temporal aspect of the wound. No skin should be removed from the medial two-thirds of the eyelid in the vast majority of cases. The skin resection should always be conservative.
17. The skin edges are then re-apposed using interrupted 7–0 Vicryl sutures.
18. The traction suture is removed.
19. The upper lid blepharoplasty wound is closed with interrupted 7–0 Vicryl sutures.

Post-operative care

Post-operatively the patient is prescribed a topical antibiotic ointment to the upper and lower lid wounds

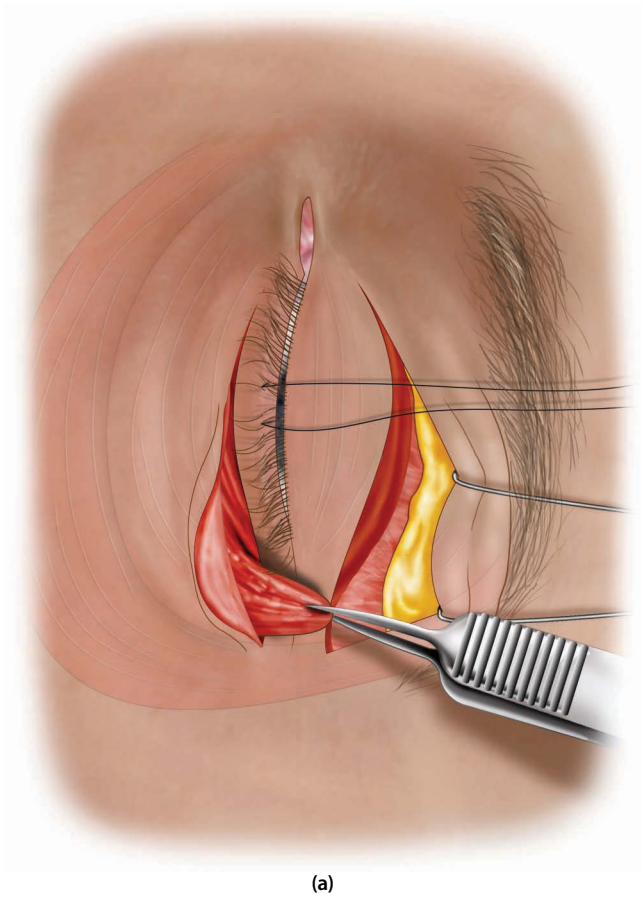


Figure 87.42 **(a)** Diagram demonstrating the creation of an orbicularis oculi muscle flap. **(b)** Intra-operative photograph showing a triangular flap of orbicularis oculi muscle being held with forceps. The redundant skin has been folded back on itself.

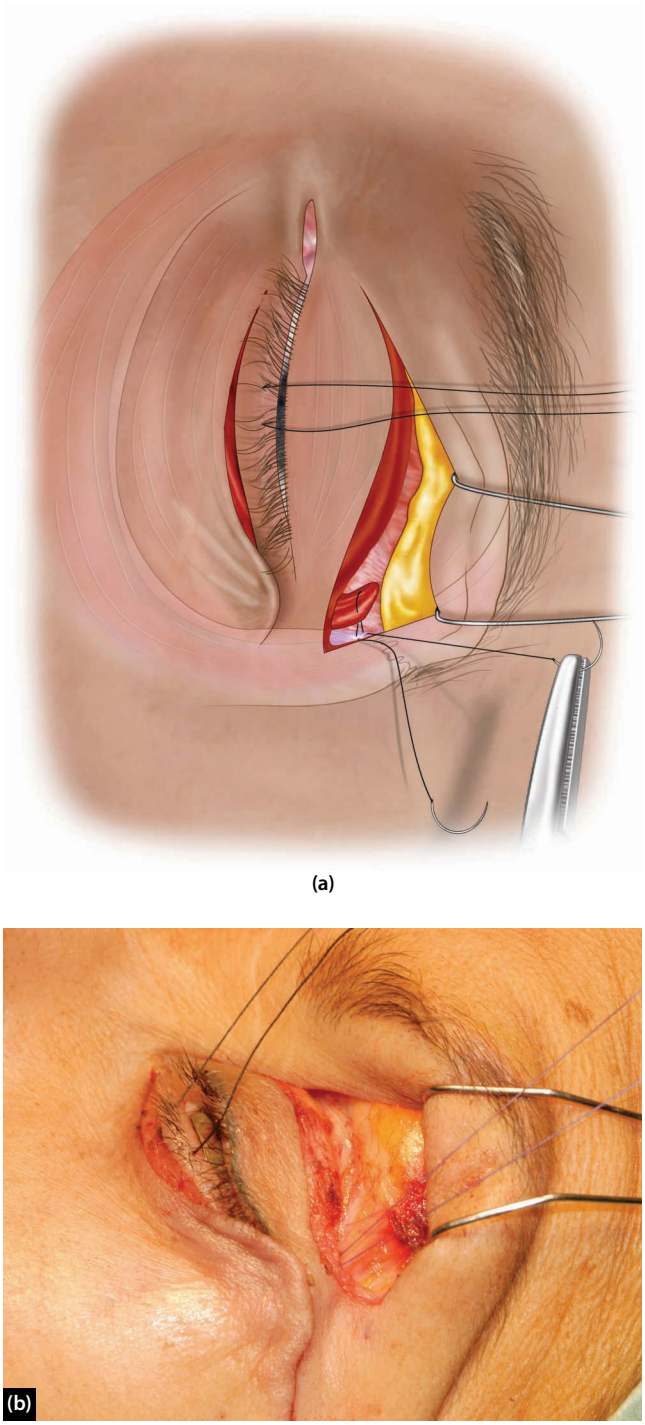


Figure 87.43 **(a)** Vicryl sutures with the attached orbicularis flap are passed beneath the intact bridge of skin and muscle laterally. The sutures are passed through the periosteum of the superolateral orbital margin. **(b)** Intra-operative photograph demonstrating the effect achieved when tension is applied to the sutures which are attached to the orbicularis flap.

three times a day for 2 weeks and Lacri-Lube® ointment 1–2 hourly to the eyes for 48 hours and at bedtime. The Lacri-Lube® ointment is then changed to a preservative-free topical lubricant gel to be used hourly during the day and Lacri-Lube® is continued at bedtime until the degree of lagophthalmos has improved. The frequency of the lubricants is then gradually reduced over the course of the next few weeks. The patient is instructed to sleep with the head of the bed elevated for 4 weeks and to avoid lifting any heavy weights for 2 weeks. Clean cool packs are gently applied to the eyelid intermittently for 48 hours. The patient should be reviewed in clinic within 2 weeks

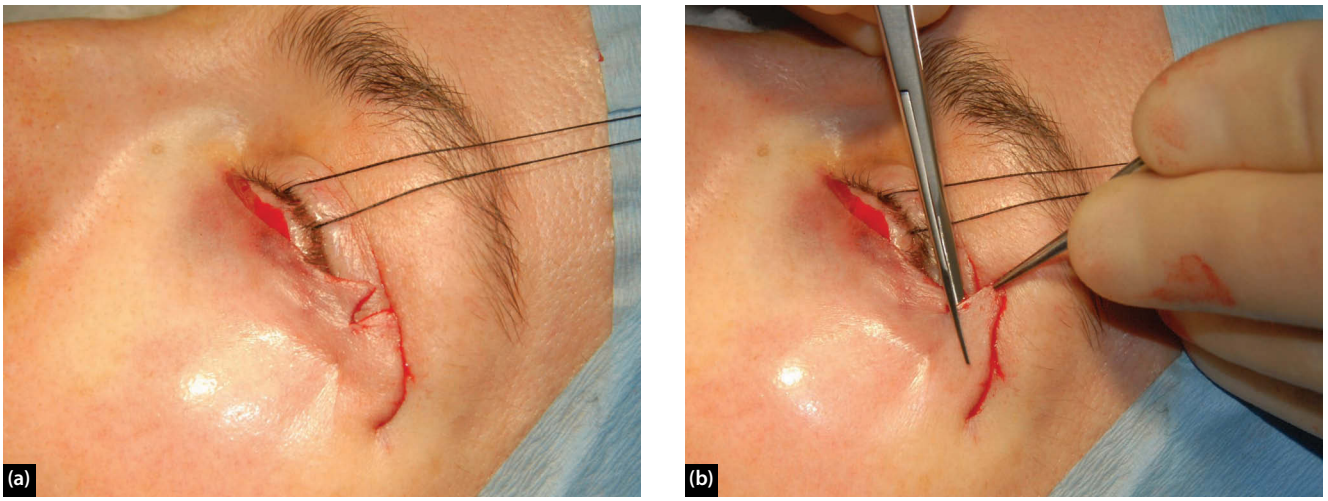


Figure 87.44 **(a)** A vertical incision is made in the central aspect of the lateral skin flap with straight iris scissors. **(b)** The excess skin is trimmed keeping some tension on the lower lid traction suture to prevent an inadvertent over-resection of skin.

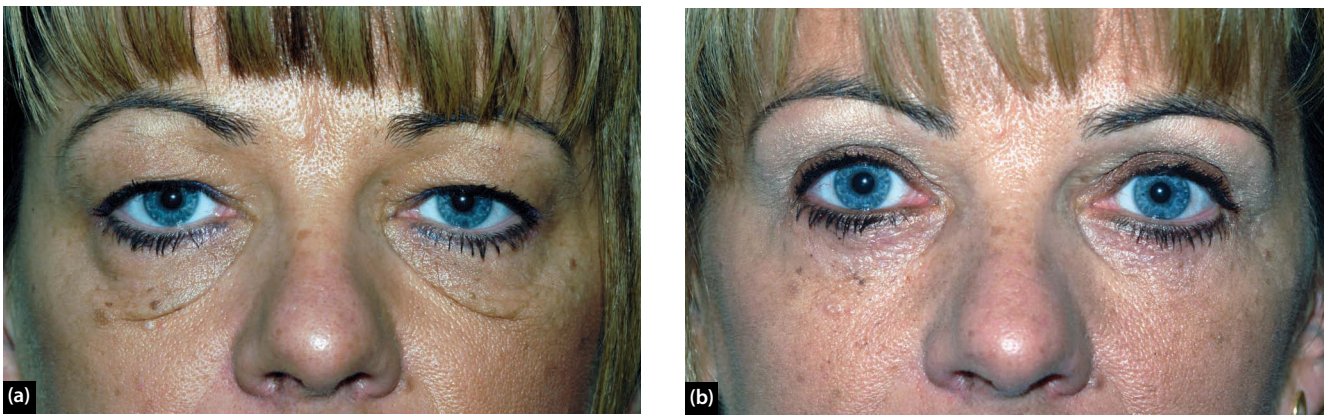


Figure 87.45 **(a)** Pre-operative appearance. **(b)** Post-operative appearance 4 months after undergoing a bilateral upper lid blepharoplasty with sculpting of the medial and central fat pads, and a bilateral lower lid transcutaneous blepharoplasty with an arcus marginalis release, fat repositioning and an orbicularis oculi muscle suspension.

and again within 4–6 weeks. The upper and lower lid skin sutures are removed at 10–14 days post-operatively. The patient is instructed to commence massage to the lower eyelids 2 weeks post-operatively. The patient should apply Lacri-Lube® ointment to the skin and massage in an upward direction for 2–3 minutes three times a day for 4–6 weeks. This is important to help to avoid lower eyelid retraction.

An example of a patient who has undergone this procedure is shown in **Figure 87.45**.

For patients who also have mild malar mounds, the lower eyelid transcutaneous blepharoplasty can be combined with a SOOF lift using the same incisions. Likewise, for patients with malar bags and a midface ptosis with descent of the malar fat pads, the transcutaneous blepharoplasty can be combined with a midface lift, again using the same incisions (**Figure 87.46**).

STRUCTURAL FAT GRAFTING

If structural fat grafting to the cheeks, temples or other facial areas is to be undertaken in conjunction with a lower eyelid blepharoplasty, this should be undertaken initially. It is important that the fat is injected as soon as possible after it has been harvested. This increases its chances of survival. The fat should be placed at different depths in the tissues by injecting only 0.1 mL of fat with each pass of the cannula. Multiple passes are required. The injection technique should be meticulous.

SOOF LIFT

Surgical procedure

1. This is undertaken after repositioning or removing lower eyelid fat.
2. The SOOF is mobilized by dissecting in the preperiosteal plane using blunt-tipped Westcott scissors, taking care to avoid damage to the infraorbital neurovascular bundle.
3. The SOOF is then sutured to the arcus marginalis and the periosteum of the lateral orbital margin with 4-0 Vicryl sutures (**Figure 87.47**).
4. The blepharoplasty is then completed as described above.

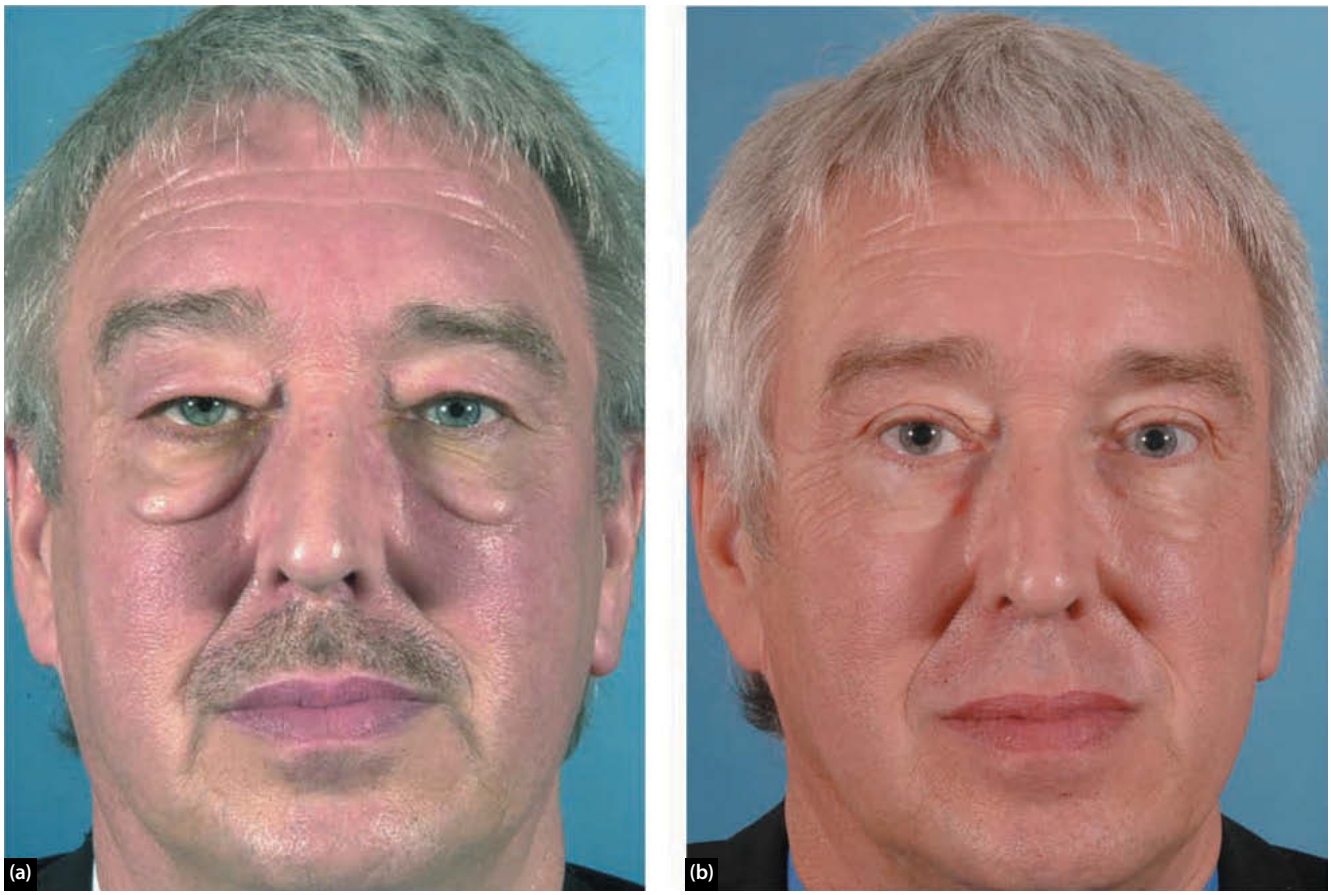


Figure 87.46 (a) The pre-operative appearance of a patient with marked bilateral lower eyelid festoons and bilateral upper eyelid dermatochalasis with no evidence of thyroid eye disease or other predisposing systemic disorder. **(b)** The post-operative appearance of the same patient 1 year following a bilateral upper lid blepharoplasty and transblepharoplasty internal browpexy and bilateral lower eyelid transcutaneous blepharoplasties combined with an orbicularis oculi muscle suspension. Note that this patient still has some lower lid festoons, which are extremely difficult to eradicate completely.

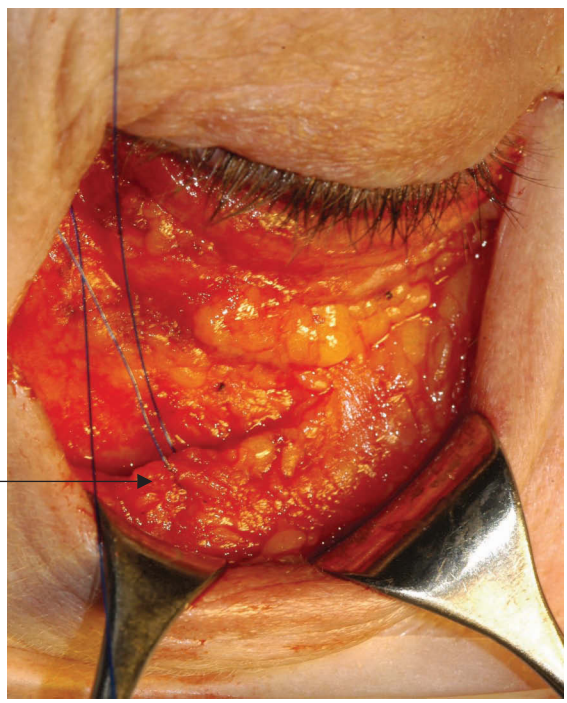


Figure 87.47 A 4-0 Vicryl suture has been placed through the SOOF.

MIDFACE LIFT

Surgical procedure

1. This is undertaken after repositioning or removing lower eyelid fat medially.
2. The periosteum is incised 2 mm below the inferior orbital margin and a subperiosteal dissection is performed using a Freer periosteal elevator, over the surface of the maxilla and zygoma, taking care to avoid damage to the infraorbital neurovascular bundle.
3. The periosteum is divided close to the buccal sulcus using Stevens scissors or the sharp end of a Freer periosteal elevator. In some patients, a buccal sulcus incision can be used to aid the subperiosteal dissection and mobilization of the midface.
4. Next, the periorbita is raised over the inferior and inferolateral orbital margin and into the orbit for a few millimetres using the Freer periosteal elevator.
5. Two or three drill holes are made through the inferior and inferolateral orbital margin, protecting the orbital contents with a malleable retractor.
6. A 3-0 Prolene suture is passed through the superior edge of the mobilized periosteum and through the ptotic malar fat pad. This suture is then passed

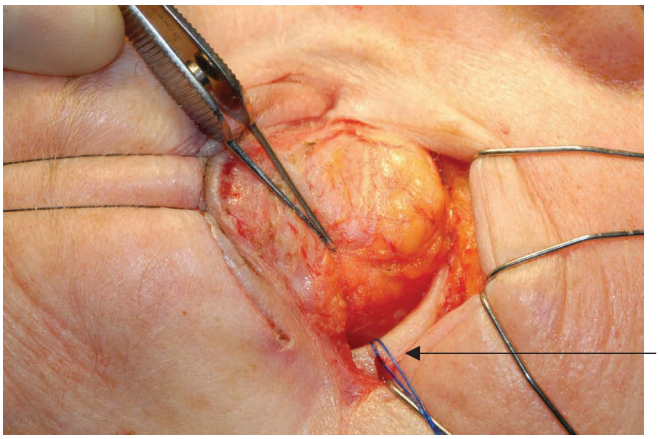


Figure 87.48 A 3-0 Prolene suture has been passed through a drill hole in the inferolateral orbital margin.

through the drill holes in the bony margin and tied (**Figure 87.48**). The suture knot is rotated into the drill hole. Additional sutures are placed as required.

7. The blepharoplasty is then completed as described above.

As an alternative option, the ptotic midface can be lifted with the use of a midface Endotine implant although this adds considerable expense to the procedure. The implant is positioned so that the tines at the inferior end of the implant engage the ptotic cheek fat pad and the other end is fixated to the lateral orbital margin using one or two titanium screws or biodegradable screws (**Figure 87.49**). The stem of the implant is then severed just above the securing screw using a 15 Bard Parker blade.

The Endotine implant gradually biodegrades over a period of approximately 6–9 months. The implant can provide a very powerful and effective midface lift. The patient should be warned that a midface lift can result in considerable post-operative swelling which can take 2–3 months to subside.

Post-operative care

This is as described above.

CHEEK IMPLANT

Although a variety of cheek implants are available (e.g. Medpor), and these can certainly provide augmentation of the midface, the author does not advocate the use of any cheek implants as these can lead to an unsatisfactory appearance after the patient has developed age-related soft-tissue deflation in the area overlying and adjacent to the implant after some years.

TRANSCUTANEOUS BLEPHAROPLASTY WITH FAT DEBULKING

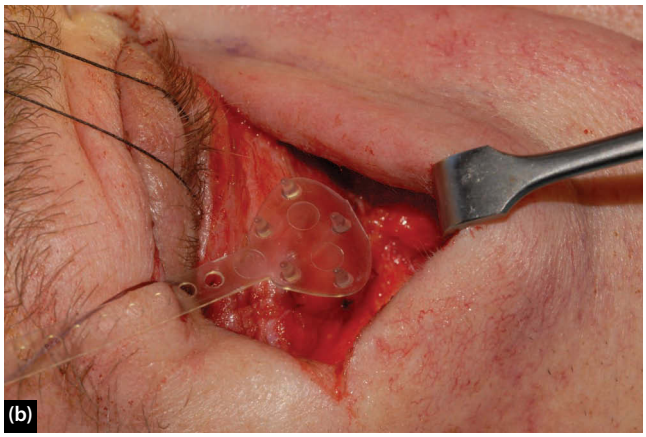
For the majority of patients seeking a lower lid blepharoplasty, usually in the age group 45–60 years of age, the transcutaneous blepharoplasty with arcus marginalis release, fat repositioning and an orbicularis oculi muscle suspension provides a very good cosmetic result with minimal risks. It is, however, time-consuming. For older patients with greater degrees of fat herniation, the fat will need to be formally debulked, paying very careful attention to haemostasis and avoiding traction on the fat. In such patients, a transcutaneous approach gives excellent access to the lower lid fat pads, which can be debulked with a very conservative removal of skin. An orbicularis muscle sling can be avoided but a lateral tarsal strip procedure will usually be required. This procedure is quicker to perform and the patients who are suitable for this procedure tend to be less demanding and critical of slight asymmetries.

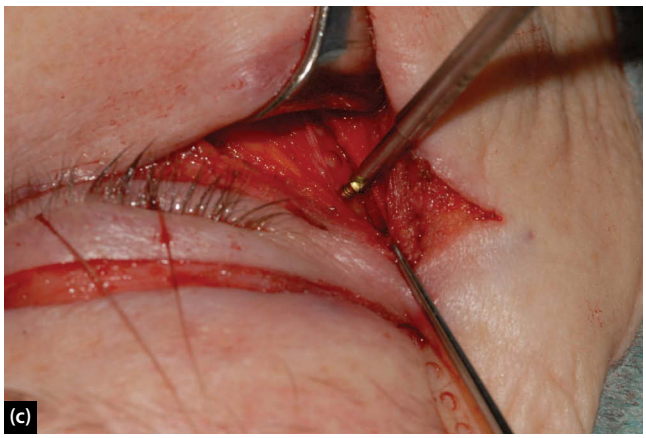
These older patients should also be carefully screened for systemic comorbidities, including undiagnosed essential hypertension. Such patients are at an increased risk of a retrobulbar haematoma with its potential visual morbidity.

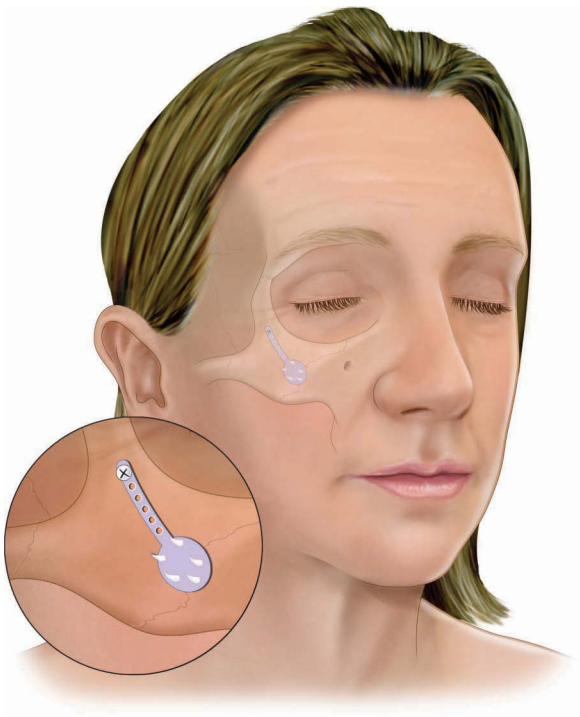
Steatoblepharon refers to a situation, usually in an older patient, where the orbital septum has become very lax with marked herniation of the lower eyelid fat pads (**Figure 87.50**). This can occasionally occur in younger patients as a familial trait. In older patients it tends to accompany dermatochalasis, eyelid laxity and ptosis. Prolapse of fat through a weakened Tenon's capsule may also accompany steatoblepharon. This fat can be resected via a lateral vertical conjunctival incision made directly over the prolapsed fat using Westcott scissors. The superolateral fornix should be avoided to prevent intraoperative damage being caused to the lacrimal gland ductules.

TRANSCONJUNCTIVAL BLEPHAROPLASTY

A transconjunctival blepharoplasty is ideally suited to the younger patient who has mild to moderate lower eyelid fat herniation but with no or minimal skin or eyelid laxity. It is also suited to the patient with thyroid eye disease and can be combined with an orbital decompression procedure. For patients who have marked fat pad enlargement, the fat can be debulked but, for patients with lesser degrees of fat herniation and who are concerned about the appearance of lower eyelid dark circles due to tear trough defects, fat can be repositioned over the inferior orbital margins.

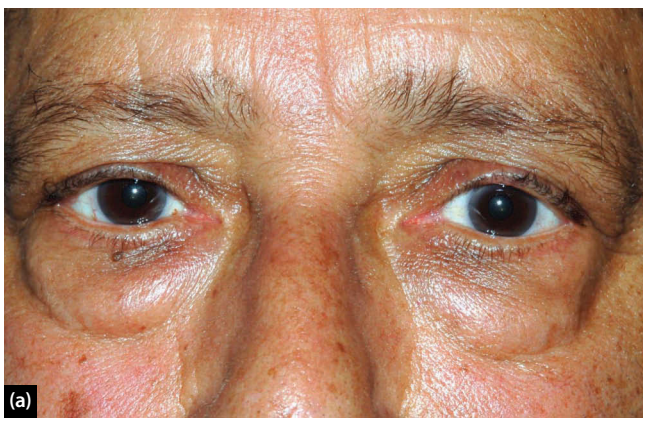






(d)

Figure 87.49 **(a)** The head of the midface Endotine implant with the protruding tines. **(b)** The implant is about to be placed. **(c)** The implant has been placed. The stem of the implant has been passed under the lateral canthal raphé and brought out through the upper eyelid wound in this example. The stem is then pulled in a superolateral direction until the desired height and contour of the midface have been achieved. The stem is being secured to the lateral orbital margin with a 1.5 × 4 mm titanium screw. **(d)** Drawing showing the location of the Endotine implant.



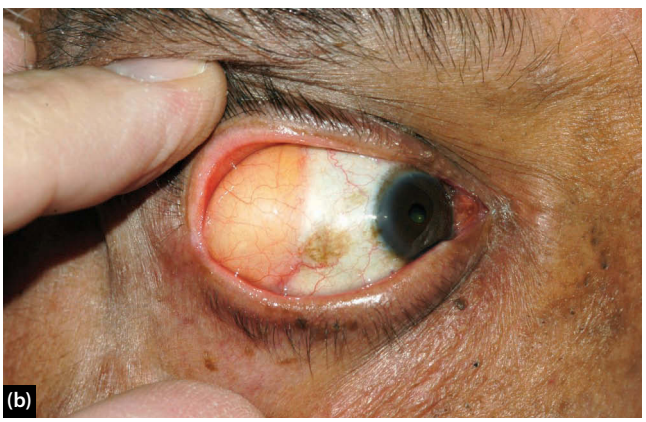


Figure 87.50 **(a)** Steatoblepharon and upper lid dermatochalasis. **(b)** A prolapse of orbital fat through a weakened Tenon's capsule in the same patient.

The patient should be warned pre-operatively that post-operative chemosis is to be expected following this surgical approach, particularly in the patient with pre-operative conjunctivochalasis, and that this usually takes 1–2 weeks to resolve. In some patients, however, it can take several weeks to resolve.

Surgical procedure

The patient is examined in a sitting position and the prolapsed preaponeurotic fat pads are outlined using gentian violet. It is particularly important to outline a lateral fat pad as the position of the fat pad and the extent of the prolapse can be difficult to judge following the injection of local anaesthetic solution and with the patient in a semi-recumbent position.

Fat repositioning

1. Approximately 2–3 mL of 0.5% marcain with 1:200 000 units of adrenaline mixed 50:50 with 2% lignocaine with 1:80 000 units of adrenaline are injected with a single injection just beneath the skin along the lower eyelid just below the tarsus. The needle is inserted temporally and advanced nasally while slowly injecting the solution. Immediate pressure is applied. A pause of 10 minutes is allowed for the adrenaline to take effect. Local anaesthetic containing adrenaline is not injected subconjunctivally to avoid its effect on the pupil.
2. The patient is prepped and draped.
3. A 4-0 silk traction suture is placed through the grey line of the lower eyelid and everted over a medium Desmarres retractor.
4. A conjunctival incision is made with a Colorado needle 3–4 mm below the inferior border of the tarsus from the level of the punctum to the lateral canthus entering the plane between the orbital septum and the orbicularis oculi muscle. The orbital fat will remain contained behind the orbital septum as long as the incision is made above the line of fusion of the septum and the capsulopalpebral fascia.
5. 4–0 silk traction sutures are placed through the medial and lateral edges of the conjunctiva and the lower eyelid retractors and fixated to the head drapes using small curved artery clips in order to protect the cornea (see **Figure 87.44a**).
6. Dissection proceeds down the plane between the septum and the orbicularis and onto the anterior surface of the infraorbital rim. This bloodless dissection is greatly aided by the use of the Colorado needle.
7. A pocket is created beneath the orbicularis muscle over the anterior lacrimal crest.
8. The arcus marginalis is incised with the Colorado needle from medial to lateral along the infraorbital rim, taking care to avoid the inferior oblique muscle medially (located directly behind the medial third of the septum) and the lateral canthal tendon laterally (**Figure 87.51**).
9. Next a double-armed 4-0 Prolene suture is passed through the prolapsed fat medially. The needles are passed beneath the orbicularis muscle over the anterior lacrimal crest medially, through the full thickness of the eyelids to exit through the skin and are then tied over a silicone bolster, pulling the fat forwards and the orbicularis upwards over the inferior orbital margin. Further sutures are placed and passed just anterior to the periosteum over the anterior surface of the inferior orbital margin centrally and laterally (**Figure 87.52**).
10. The conjunctival retraction sutures are removed and the conjunctiva and eyelid retractors are re-apposed with 2–3 interrupted 7.0 Vicryl sutures.

An example of a patient who has undergone this procedure is shown in **Figure 87.53**.

Post-operative care Post-operatively the patient is prescribed a topical antibiotic ointment to the eyes three times a day for 2 weeks and Lacri-Lube® ointment 2 hourly to the eyes for 48 hours and at bedtime. The Lacri-Lube® ointment is then changed to a preservative-free topical lubricant gel to be used 2 hourly during the day and Lacri-Lube® is continued at bedtime until any

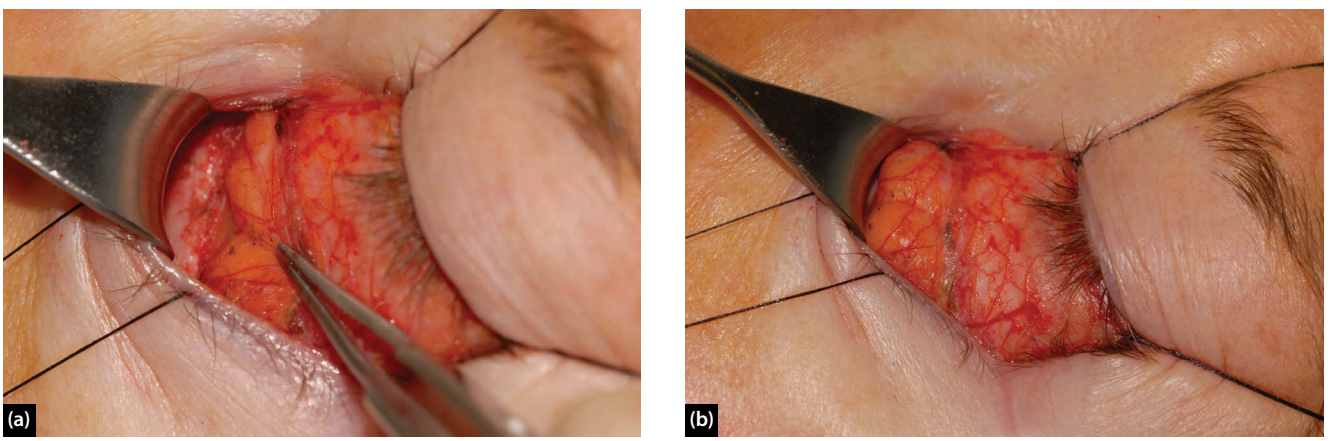


Figure 87.51 **(a)** The arcus marginalis has been opened allowing the preaponeurotic fat to prolapse. The inferior orbital margin has been exposed. **(b)** The fat is now prolapsing over the inferior orbital margin prior to placement of the double-armed Prolene sutures.

post-operative chemosis has resolved. Post-operative steroid drops are unnecessary. The patient is instructed to sleep with the head of the bed elevated for 2 weeks and to avoid lifting any heavy weights for 2 weeks. Clean cool packs are gently applied to the eyelid intermittently for 48 hours. The patient should be reviewed in clinic within 5 days when the Prolene sutures are removed, and again within 4–6 weeks. The conjunctival sutures should drop out spontaneously within 2 weeks. Massage to the lower eyelid/cheek junction for 3 minutes three times per day can be commenced using Lacri-Lube® ointment as soon as the Prolene sutures have been removed. This is continued for 2–3 weeks.

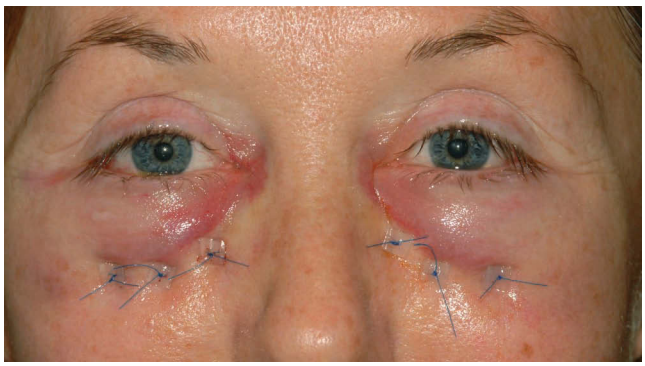


Figure 87.52 Three 4-0 double-armed Prolene sutures have been passed from the fat through the full thickness of the lower eyelids and tied over silicone bolsters.

Fat removal

In patients with a true fat excess a more traditional fat resection is required. In these patients gentle pressure is applied to the globe to allow the orbital fat pads to herniate into the wound.

The operation is as per stages 1–5 for fat repositioning above.

6. The orbital septum is opened using the Colorado needle over the points of maximum convexity caused by the bulging of the fat with pressure applied to the globe. The fat will prolapse through the openings in the septum.
7. The fat is then very carefully excised after clamping the fat with a curved artery clip. Strict attention is paid to meticulous haemostasis (**Figure 87.54**).
8. No undue traction should be exerted on the fat. The fat is removed commencing with the nasal fat pad, moving to the central and then to the lateral fat pads.
9. The residual fat should be left flush with the orbital margin to prevent over-resection with a subsequent 'skeletonized' look.

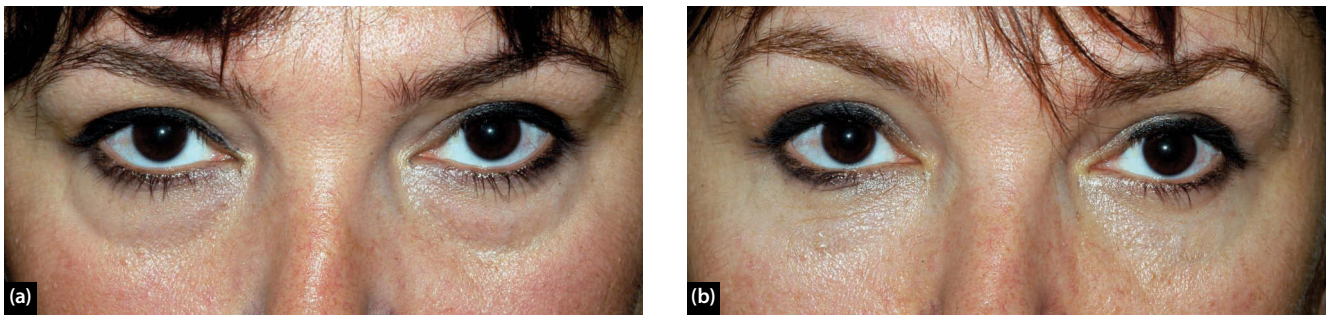


Figure 87.53 (a) Pre-operative appearance. **(b)** Post-operative appearance following a bilateral lower lid transconjunctival blepharoplasty with arcus marginalis release and fat repositioning.

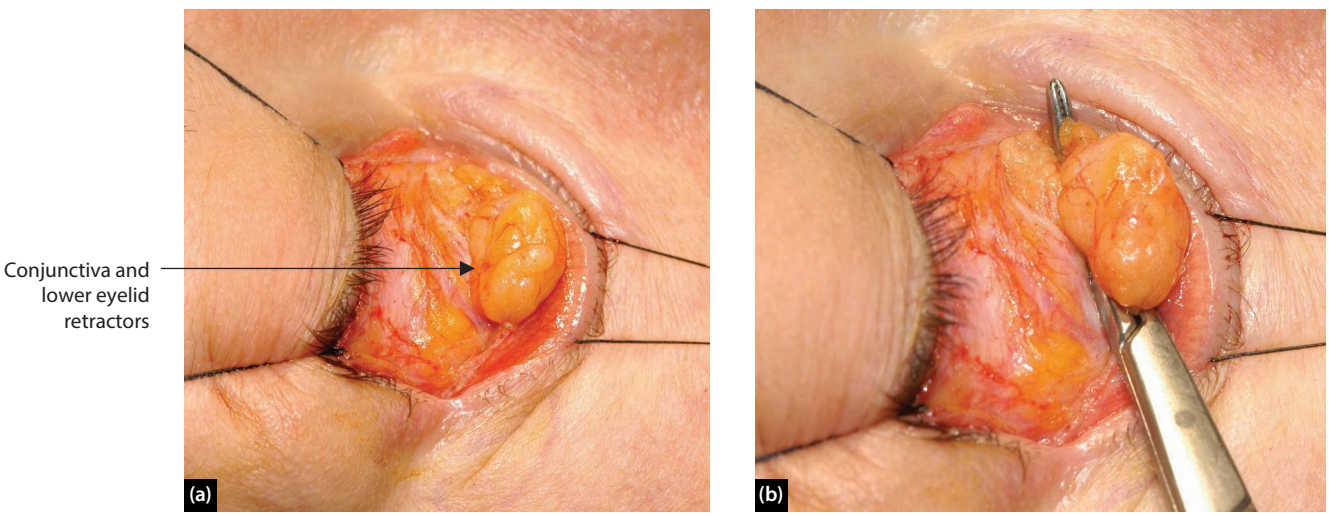


Figure 87.54 (a) The central eyelid fat pad has prolapsed into the wound after opening the orbital septum. **(b)** The central fat pad has been clamped with a curved artery clip.

10. The Desmarres retractor is removed and the eyelids inspected to ensure adequacy of fat removal and symmetry. If there is concern that too much fat has been removed, this can be replaced as a free graft over the inferior orbital margin.
11. The conjunctival retractor sutures are removed and the conjunctiva and eyelid retractors are reapposed with two or three interrupted 7-0 Vicryl sutures.

An example of a patient who has undergone this procedure is shown in **Figure 87.55**.

In some patients a minimal skin excess can be addressed at this stage by adding a simple 'pinch' skin resection. The lower lid skin is gently pinched into a fold in the lateral aspect of the eyelid using Castroviejo 0.3 mm toothed forceps and this is marked out using a cocktail stick impregnated with gentian violet solution, ensuring that the eyelid position is not affected even with upgaze and with mouth opening. The skin alone is resected with a Colorado needle and the skin edges reapproximated with interrupted 7-0 Vicryl sutures.

Post-operative care Post-operatively the patient is prescribed a topical antibiotic ointment to the eyes three times a day for 2 weeks and Lacri-Lube® ointment 2 hourly to the eyes for 48 hours and at bedtime. The Lacri-Lube® ointment is then changed to a preservative-free topical lubricant gel to be used 2 hourly during the day and Lacri-Lube® is continued at bedtime until any post-operative chemosis has resolved. Post-operative steroid drops are unnecessary. The patient is instructed to sleep with the head of the bed elevated for 2 weeks and to avoid lifting any heavy weights for 2 weeks. Clean cool packs are gently applied to the eyelid intermittently for 48 hours. The patient should be reviewed in clinic within 2 weeks, and again within 4–6 weeks. The conjunctival sutures should drop out spontaneously within 2 weeks. If a pinch skin excision has been performed, the skin sutures are removed in clinic after 2 weeks.

PATIENT AFTERCARE

If the surgery has been performed under general anaesthesia, it is wise to apply a compressive dressing for 30 minutes until the patient has recovered. This prevents oozing into the eyelids if the patient performs a Valsalva manoeuvre following extubation. The dressings are then removed and ice packs applied intermittently for 24–48 hours post-operatively. Significant post-operative pain is rare, and most patients are comfortable with a mild non-aspirin analgesic. Significant post-operative pain should, however, raise concerns about the possibility of a retrobulbar haemorrhage and the patient should be examined to ensure that this has not occurred.

Increased pigmentation from haemosiderin deposition is sometimes observed in patients with excessive bruising. To minimize this post-operative problem, patients should be instructed to avoid post-operative sun exposure until the ecchymosis has completely resolved.

Eyelids are extremely sensitive to allergenic insult, and any pre-existing atopy can be aggravated by surgery. Patients should therefore not use cosmetics for at least 10 days after surgery in order to avoid an allergic reaction. Mineral make-ups can be used 10–14 days post-operatively. Patients should also be made aware of the symptoms and signs of allergy to topical antibiotic ointments prescribed for application to the wounds at home after discharge.

For patients who have undergone a more extended lower eyelid blepharoplasty with resuspension of the orbicularis oculi muscle and a SOOF or midface lift, the patient and surgeon must be prepared to wait several weeks for post-operative swelling to resolve and healing to take place before judging the final outcome, since a complete recovery takes significantly longer after this procedure than after a more traditional blepharoplasty. Pre-operative counselling of the patient is vital to ensure that such a prolonged period of convalescence is acceptable to the individual patient.

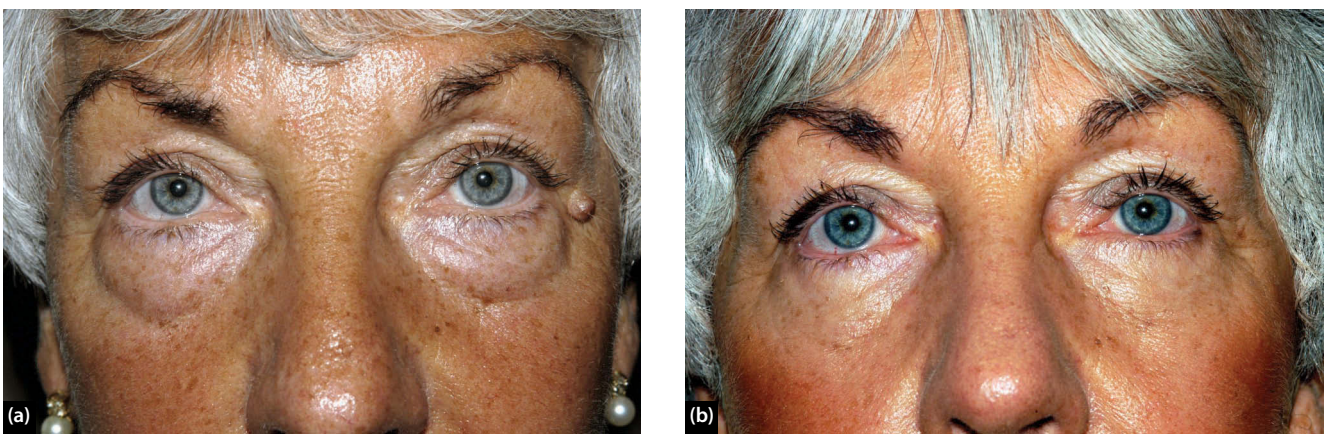


Figure 87.55 **(a)** Pre-operative appearance. **(b)** Post-operative appearance of the same patient 12 months following a bilateral transconjunctival blepharoplasty with fat debulking and removal of a left lateral canthal skin lesion.

COMPLICATIONS OF BLEPHAROPLASTY SURGERY

A number of complications can occur following blepharoplasty surgery (**Box 87.1**). Fortunately, serious complications are rare. The vast majority of complications are ophthalmic in nature and for this reason an increasing number of well-informed patients requesting blepharoplasty surgery seek the skills of appropriately trained and experienced oculoplastic surgeons for their pre-operative evaluation and for their surgery.

BOX 87.1 Complications of blepharoplasty

1. Blindness
2. Bradycardia or other dysrhythmias from the oculocardiac reflex
3. Dry eye
4. Lower eyelid retraction
5. Lower eyelid ectropion
6. Rounding of the lateral canthus
7. Hollowing of the eyelids
8. Epiphora
9. Lagophthalmos
10. Asymmetrical upper lid creases
11. Diplopia
12. Blepharoptosis
13. Chemosis
14. Corneal abrasion
15. Injury to branches of the facial nerve
16. Sensory loss in the distribution of the infraorbital or zygomaticofacial nerves
17. Irregular lower eyelid lumps
18. Fat necrosis

Many of these complications can be avoided by careful pre-operative patient evaluation and selection of the most appropriate surgical procedure for the patient, as outlined above.

- **Blindness** is by far the most serious complication of blepharoplasty surgery. This is usually due to the sudden occurrence of a post-operative orbital haemorrhage. Although rare (the precise incidence is unknown due to under-reporting of this complication but is estimated to be approximately 0.05%), this is a devastating complication of an operation performed most commonly to improve a patient's cosmetic appearance. The patient should be counselled about such a risk pre-operatively. The surgery must be meticulously performed with strict attention to intraoperative haemostasis. Undue traction on orbital fat must be avoided. It is important to ensure that all risk factors for bleeding are addressed pre-operatively. No patient should undergo blepharoplasty surgery involving the removal of orbital fat if hypertension is uncontrolled, if there is a history of a bleeding disorder or if the patient is taking antiplatelet drugs. The patient must be given post-operative instructions about restrictions on activity following surgery. The patient must be able to return to hospital immediately in the event of any sudden orbital pain, proptosis or decrease in vision. The patient with a retrobulbar haematoma usually complains of a steady, lancinating pain, similar to that of glaucoma. The patient may also report scintillating scotomas or complete visual loss and may exhibit mydriasis with a relative afferent pupil defect, proptosis with resistance to retropulsion, and haemorrhagic chemosis.

  If a patient develops a sudden orbital haemorrhage with proptosis, subconjunctival haemorrhage and decreased visual acuity, the wound must be opened immediately to drain the haematoma and a lateral canthotomy and inferior cantholysis should be performed to achieve an emergency orbital decompression. Because the consequences of a retrobulbar haemorrhage are so severe, aggressive intervention is required. If possible the surgeon should not wait for signs of optic nerve compression (i.e. reduced visual acuity, visual field loss, an afferent pupillary defect) to arise, because permanent damage may have occurred by that time. Rather, excessive pain and proptosis necessitate immediate surgical decompression. The incision should be opened and carefully explored. Medical decompression of the orbit with corticosteroids (methylprednisolone 100 mg i.v.), carbonic anhydrase inhibition (acetazolamide 500 mg i.v.) should be organized straight away and, if necessary, osmotic diuresis (mannitol 50–100 g i.v. over 30 minutes) may also be used. The patient's intraocular pressure should be monitored using a Perkins tonometer or a Tonopen and the patient's fundus should be examined to ensure patency of the central retinal artery.
- The **oculocardiac reflex**, characterized by intraoperative bradycardia or dysrhythmia, can be triggered by traction on the extraocular muscles or orbital fat pads. A profound bradycardia or even asystole can occur. Younger patients are more susceptible to the severe effects of this reflex. The anaesthetist monitoring the patient should be aware of the possibility of a dysrhythmia occurring and should alert the surgeon who should in turn release any tissue to which traction is being applied. Atropine or glycopyrolate should be kept drawn up in a syringe and available immediately in the event of a severe dysrhythmia.
- **Keratoconjunctivitis sicca (dry eye syndrome)** is most often seen in patients who have a pre-existing tear film insufficiency. This should be specifically examined for pre-operatively and the patient counselled accordingly. This can be particularly important in patients who have undergone corneal refractive procedures (e.g. LASIK) or who wear contact lenses. The consistent continued use of frequent artificial tears is imperative in these patients who may also require additional procedures at a later date (e.g. punctal plug placement or punctal cautery). Patients who require artificial tears more frequently than three or four times per day should use a preservative free preparation.

- Mild **lower eyelid retraction** may be managed conservatively with post-operative eyelid massage. The eyelid should be massaged in an upward direction after applying Lacri-Lube® ointment to the skin. A SOOF lift or midface lift combined with a lateral canthal resuspension may prevent the need for a full-thickness skin graft following an over-resection of skin leading to lower eyelid retraction. Middle lamellar contracture resulting in lower eyelid retraction (see **Figure 87.16**) may, however, require division of the scar tissue and placement of a hard palate graft or a dermal graft.
- A temporary **lower eyelid ectropion** can occur, particularly laterally, as a result of post-operative wound oedema, wound contraction and/or hypotonicity of the orbicularis oculi muscle. A frank ectropion occurs when significant lower eyelid laxity has not been addressed or where caution has not been exercised in resetting of the orbital septum or in the degree of skin resection. This will usually require a lateral canthal tightening procedure and in some patients this will have to be combined with a skin graft.
- **Rounding of the lateral canthus** occurs following the excessive resection of skin and orbicularis oculi muscle as a triangle laterally, particularly in a patient whose eyelid laxity has not been appropriately addressed. This can prove to be very challenging to correct, and may require a midface lift combined with a lid-tightening procedure.
- **Hollowing of the eyelids** occurs if too much orbital fat is removed, particularly in older patients with very thin eyelid skin. In the lower eyelids care should be taken to resect the fat flush with the inferior orbital margin and to avoid pulling the fat anteriorly during the resection. In general, fat removal from the upper eyelids should be avoided wherever possible. Hollowing of the eyelid can be addressed by the placement of fat pearls harvested from the periumbilical area, or by means of structural fat grafting.
- **Epiphora** is common in the first few post-operative days. Corneal irritation, which triggers hypersecretion of tears, and lower eyelid ectropion, which removes the inferior punctum from the surface of the globe, usually causes epiphora. Continued epiphora following blepharoplasty surgery may occur as a consequence of lagophthalmos with a secondary punctate keratopathy and hypersecretion of tears and/or a malposition of the inferior punctum. A subtle vertical positioning of the inferior punctum may result in epiphora. This is seen on careful slit lamp examination and may occur some years after surgery as the lower eyelid tarsoligamentous support becomes more lax. Conjunctivochalasis, a redundant fold of bulbar conjunctiva, may lie over the inferior punctum obstructing tear flow. This is again a subtle abnormality requiring careful slit lamp examination. It can respond to a conservative resection of the redundant conjunctiva. Persistent epiphora due to malposition of the inferior punctum requires further surgery to reposition the punctum.
- **Lagophthalmos** following an upper eyelid blepharoplasty is avoided by ensuring a conservative skin resection in the upper eyelids. Overzealous resection may require a skin graft if exposure symptoms do not respond to conservative treatment.
- The **appearance and symmetry of the upper eyelid skin creases** have a profound effect on the cosmetic outcome of an upper eyelid blepharoplasty. The skin crease should be higher in a female and well defined in contrast to a male in which this should be lower and more subtle. Complications are avoided by meticulous pre-operative planning and marking. Post-operatively it is easier to raise a skin crease which is unsatisfactory than it is to lower it.
- **Diplopia** is a rare complication following lower eyelid blepharoplasty. This is usually due to surgical trauma to the inferior oblique muscle. A good knowledge of anatomy, a meticulous surgical dissection and an avoidance of the excessive use of cautery should prevent such a complication. A permanent ocular motility disturbance caused by blepharoplasty is much rarer than a pre-existing phoria, which may decompensate following surgery. For this reason it is imperative to perform a detailed pre-operative ophthalmic examination in order to diagnose the problem and to protect the surgeon from unfair blame.
- **Blepharoptosis** may occur if the levator muscle, the horns of the levator muscle complex or Whitnall's ligament are damaged during surgery. These should be carefully identified and avoided. Any pre-existing ptosis should be addressed at the time of an upper eyelid blepharoplasty by means of a levator aponeurosis advancement. This should be performed under local anaesthesia to facilitate an intra-operative adjustment of the height and contour of the upper eyelid(s) with the benefit of the patient's cooperation.
- **Chemosis** (**Figure 87.56**), which is more commonly seen following a transconjunctival blepharoplasty, usually resolves after 10–14 days following the liberal use of topical lubricants. On very rare occasions it may last for some weeks post-operatively. The use of topical steroids to treat this should be avoided

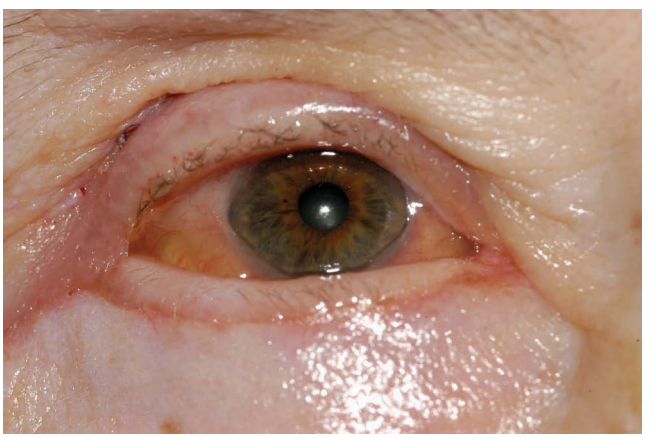


Figure 87.56 Post-operative conjunctival chemosis following a transcutaneous lower eyelid blepharoplasty.

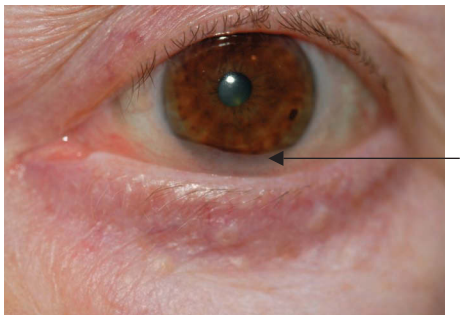


Figure 87.57 Conjunctivochalasis.

because of the risk of cataract, glaucoma and predisposition to infection. If the chemosis does not resolve, a redundant fold of forniceal conjunctiva may need to be removed and the cut edges sutured to the episclera using 8-0 Vicryl sutures. The occurrence of post-operative chemosis can be predicted in the patient who has pre-operative conjunctivochalasis (**Figure 87.57**). Such a patient should undergo the simultaneous resection of the redundant conjunctiva at the time of the blepharoplasty.

- All precautions must be taken to prevent a **corneal abrasion**, which can be extremely painful. Care should be taken when placing eyelid and conjunctival traction sutures to avoid causing a corneal abrasion. Most corneal abrasions heal rapidly without any long-term sequelae but in some patients a recurrent corneal abrasion syndrome can occur. Diabetic patients and patients with corneal dystrophies (which may have been previously undiagnosed) are at particular risk of a recurrent corneal abrasion syndrome. If an abrasion does occur, the patient must be treated with frequent topical antibiotics and should undergo a daily review with slit lamp examinations until the abrasion has completely healed. A topical lubricant ointment should be prescribed at night for a minimum period of 6 weeks to help prevent a recurrent corneal abrasion syndrome.
- **Injury to branches the facial nerve**, particularly the zygomatic branch to the inferior orbicularis, is a potential hazard of dissecting below the orbicularis oculi muscle. This can lead to a loss of tone in the muscle with loss of lower eyelid symmetry lower eyelid ectropion or lagophthalmos. A subperiosteal dissection minimizes the risk of this complication.
- **Sensory loss in the distribution of the infraorbital or zygomaticofacial nerves** is usually temporary. Care should be taken when cauterizing branches of the infra-orbital artery over the inferior orbital margin
- **Irregular lower eyelid lumps** can occur following fat repositioning. This is usually temporary and the lumps often respond to a period of post-operative massage. The use of steroid injections should be avoided.
- **Fat necrosis** is rare and manifests as small, painful, indurated nodules. Massage can hasten their resolution. Injection of steroids into the lesions is effective but carries the risk of subcutaneous atrophy and hypopigmentation.

Medicolegal pitfalls

Most complications of blepharoplasty surgery stem from an inadequate pre-operative patient evaluation. From a medicolegal perspective, a thorough history and meticulous ophthalmic examination, good documentation, informed consent with the provision of detailed information about the pros, cons, risks and potential complications and their management, and excellent patient communication are crucial.

FUTURE RESEARCH

Future research should focus on the improvements that can be made in addressing age-related facial and periocular volume deficits using refined methods of safe structural fat grafting and improvements in the quality and safety of dermal fillers, to help to achieve better and sustained results from blepharoplasty surgery.

KEY POINTS

Anatomy

- A thorough understanding of the surgical anatomy of the eyebrows, eyelids and midface is essential prior to performing a blepharoplasty.
- The distance between the inferior aspect of the eyebrow and the upper lid skin crease on downgaze should be approximately two-thirds of the distance from the inferior aspect of the eyebrow to the eyelid margin. It is important to maintain these dimensions. In general, a minimum distance of 10–12 mm should be left between the inferior aspect of the eyebrow and the upper eyelid skin crease when performing an upper lid blepharoplasty.
- It is very important to be able to distinguish the lacrimal gland from orbital fat.
- Whitnall's ligament supports the levator muscle complex and should not be disturbed during surgery.
- The inferior oblique muscle lies between the medial and central fat pads.

Blepharoplasty

- A history of contact lens wear, previous corneal laser refractive surgery, or a dry eye, facial palsy or thyroid dysfunction identifies a patient at risk of exposure keratopathy symptoms following an upper lid blepharoplasty.
- It is important to exclude a bleeding disorder, as a post-operative haemorrhage following a blepharoplasty is potentially sight-threatening. The use of aspirin or non-steroidal anti-inflammatory agents should be discontinued 2 weeks pre-operatively.
- The patient seeking or referred for a blepharoplasty should undergo a complete pre-operative ophthalmic examination and examined specifically to exclude the possibility of thyroid eye disease.
- The secondary effects of brow ptosis on the upper eyelids must be recognized.
- Pre-operative photographs must be taken. Written consent should be obtained before the photographs are taken and it should be made clear to the patient how the photographs are to be used.
- Botulinum toxin injections should not be given at the time of surgery.
- For purely elective, cosmetic procedures, the patient should be encouraged to consider the information carefully before making a decision to proceed. This may necessitate a further consultation or an attendance at a pre-assessment clinic to obtain fully informed consent and to answer any residual queries.
- The patient should not be asked to sign a consent form for an elective cosmetic procedure on the day of surgery. The risks and potential complications that have been discussed should be documented in the patient's records, on the patient's consent form and in a letter addressed to the patient. The patient should also be provided with a formal document which outlines the potential complications of blepharoplasty surgery, their management and he financial responsibilities that would be incurred.
- It should be noted that fat removal should be undertaken very conservatively, if at all, in the upper lid so as to avoid a secondary hollowing of the upper eyelid, which can result in a very aged appearance.
- No skin should be removed from the medial two-thirds of the lower eyelid in the vast majority of cases. The skin resection should always be conservative.
- Significant post-operative pain following a blepharoplasty should raise concerns about the possibility of a retrobulbar haemorrhage and the patient should be examined immediately to ensure that this has not occurred.
- By far the most serious complication of blepharoplasty surgery is blindness.

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CHAPTER
88

SURGICAL REJUVENATION OF THE AGEING FACE

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SEARCH STRATEGY

Data in this chapter may be updated by a Medline search using the keywords: rhytidectomy, facelift, facial rejuvenation, and facial fat grafting or autologous fat transfer.

INTRODUCTION

As populations expand and life expectancy increases, growing numbers of people are seeking methods to reverse the outward effects of ageing. Over the past decades, refinements in surgical techniques have enhanced our ability to achieve natural-looking results with an emphasis on facial harmony and avoidance of the stigmatized 'operated' look. This has allowed aesthetic facial surgeons to meet the high expectations of an increasingly astute patient population and permitted the practice to flourish. Central to the discussion on ageing face surgery is the evolution of facelift surgery, or rhytidectomy. This chapter will provide an overview of the history of facelift surgery and its techniques, and review the senior author's approach to ageing face surgery. The recent resurgence in interest in autologous fat grafting will also be reviewed.

HISTORY OF AGEING FACE SURGERY

The history of ageing face surgery begins with the advent of rhytidectomy, which can be traced back to the dawn of the 20th century. Average lifespans increased sufficiently around this time such that populations began to manifest recognizable signs of ageing. Existential issues of senescence became more salient in the minds of society. Confronted with this phenomenon, clinicians began honouring requests for procedures that would ostensibly slow or reverse the ageing process. Early pioneers of aesthetic plastic surgery were commonly referred to as 'featural surgeons', a pejorative reflecting the underlying sentiment of negativity towards what was considered unnecessary surgery. While many in the medical community shunned the practice of aesthetic surgery, a minority of others recognized the benefits of these procedures and practised in secret on growing numbers of hopeful patients. Unfortunately, public disdain curbed widespread acceptance of plastic surgery and stifled documentation of these early efforts.

Although there is historical debate on the matter, the German surgeon Erich Lexer (1867–1937) is frequently credited as the first individual to describe rhytidectomy, doing so in 1906. Using S-shaped incisions, Lexer excised skin paddles in strategic temporal and preauricular locations to remove lateral rhytids, or wrinkles, which became known as rhytidectomy. Skin excision was conservative and performed only to facilitate closure. Not surprisingly, Lexer's technique resulted in only a subtle improvement. In the ensuing years, other European surgeons including Hollander (1912), Passot (1919), Noel (1920) and Joseph (1921), reported their experiences treating the ageing face. American involvement in facelift surgery occurred at the same time, though virtually independently of European advancements. The first American to publish on the subject was Miller (1907), also one of the first to provide anatomical drawings guiding incision placement. Bettman (1920), another American, was the first to describe the

long incision connecting the pre- and postauricular regions that is now familiar to the modern facelift surgeon. He was also the first to present before and after photographs for publication, now a standard practice.

These early surgeries consisted primarily of limited skin excisions, with predictably limited results. The next step in the evolution of facelift surgery was the practice of wide subcutaneous elevation. This so-called 'long-flap' technique combined with Bettman's incision ushered in the era of subcutaneous rhytidectomy. The technique gained rapid popularity on account of being a technically straightforward operation with a good safety profile; however, it had significant drawbacks. Tension was placed exclusively on the skin flap, leading to a characteristic 'operated' look, and the results were also frequently short-lived due to what is now recognized biomechanically as skin creep and rebound stretching. Despite these flaws, essentially no other significant contributions were made during this early period. Innovations primarily centered on variations of the incisions, but the surgical concept remained unchanged. Subcutaneous rhytidectomy, therefore, remained the standard for nearly 50 years.

The 1970s witnessed two major advancements in ageing face surgery. The first was introduced by Skoog[1] in 1974, who demonstrated the existence of a safe dissection plane below a tough fascial layer spanning the face. His work showed that this plane is continuous with the subplatysmal plane in the neck. By developing a 'short flap' along this plane, the fascial layer could be used as a girdle to lift the skin and subcutaneous tissue together. Skoog reasoned that suspension of this composite unit would generate less tension on the skin, which translated into less visible scarring and more durable results. Indeed, subsequent biomechanical studies have demonstrated this, confirming less rebound relaxation and skin creep.[2] For the first time, Skoog demonstrated how the lower face and upper neck could be safely rejuvenated as one anatomical unit without detaching the skin.

The second major advancement was the description of the superficial musculoaponeurotic system (SMAS), by Mitz and Peyronie in 1976.[3] Their work resulted in a landmark publication confirming Skoog's fascial layer while detailing its anatomical relationship to other facial structures. They demonstrated the SMAS to be a condensed fibrous mesh layer contiguous with the platysma, situated below the subcutaneous fat and over the mimetic musculature and motor branches of the facial nerve. They also described a series of transverse fibrous septations between the SMAS and skin, allowing for the transmission of facial expression. Because the ageing process weakened elasticity of these fibrous septations, Mitz and Peyronie postulated that suspension of the SMAS could aid in re-establishing a youthful facial appearance.

These seminal works laid the foundation for modern approaches to facelift surgery, which are based on suspension of this deep layer. Modern facelifting techniques can be broadly categorized as either SMAS technique rhytidectomies or so-called 'deep plane' rhytidectomies. The SMAS rhytidectomy technique comprises a vast number of variations, from simple suture plication, to more extensive flap dissection and suspension. These techniques treat the subcutaneous and deep layers separately, as opposed to the 'composite flap' featured in deep plane techniques. SMAS procedures allowed for a more natural and durable rejuvenation, particularly of the lower third of the face, when compared to the prior generation of subcutaneous facelifts. The 'deep plane' facelift techniques arose directly from Skoog's 'short flap' technique.[4–6] The concept was pioneered by Hamra in an attempt to achieve a greater effacement of the nasolabial fold, which he felt was not adequately addressed by the SMAS techniques.[4] In the deep plane technique, dissection of the midface transitions from a subplatysmal plane to a deep subcutaneous plane in the cheek to include the malar fat pad. The transition point occurs over the zygomaticus musculature. Hamra later expanded this technique into the 'composite' facelift flap by incorporating the orbicularis oculi muscle in the flap via zygorbicular dissection through a separate subciliary incision. This was done in order to provide improvement of the malar region and address what he saw as disharmony between the adequately rejuvenated jawline and the insufficiently treated midface.

The continuing evolution of today's facelift reflects an increasing understanding of ageing in the critical midface and periorbital regions. In today's ageing face practice, surgeons seek not only to soften the nasolabial fold, but to achieve a smooth transition from the periorbital region, while re-establishing youthful fullness and projection of the cheek. A variety of techniques including suborbicularis oculi fat (SOOF) lifting, orbital fat repositioning or septal reset, and different forms of midface lifting have been developed to achieve these ends.[7–10] These innovations allow surgeons to create natural transitions between rejuvenated facial subunits as part of a balanced full-face surgical rejuvenation procedure.

A complementary though conceptually distinct approach to the ageing face from rhytidectomy is autologous fat grafting. The history of autologous fat grafting dates back to as early as 1893, when Neuber transplanted fat grafts for facial deformities resulting from tuberculous osteitis. Similar to facelift surgery, advancements in the field lay dormant until the 1970s, when a renewed interest in these techniques was born out of the advent of liposuction. Today there is a full-blown renaissance in facial fat grafting, fuelled in part by the work of Sydney Coleman and others, and a rapidly growing public interest in facial fillers in general. Coleman's lipostructure technique,[11, 12] in which large volumes of fat are injected in minute 'parcels' within the subcutaneous space, is regarded by some as a potential replacement for rhytidectomy altogether.[13] There is debate in current practice regarding technical aspects of fat harvest and transfer, but the technique is now widely accepted and in wide clinical practice. In addition, research into adipocyte biology has elucidated the presence of an abundance of growth factors and multipotent stem cells in the harvested lipoaspirates.[14] Therefore the cutting edge of fat grafting includes numerous applications in not only aesthetic surgery but also reconstructive surgery and multidisciplinary regenerative medicine.

BIOLOGY OF AGEING

Facial ageing involves a wide array of biological changes of both intrinsic and extrinsic aetiology. Atrophy is the central process of intrinsic ageing. The facial skin, subcutaneous fat and facial skeleton are each affected and contribute to the ageing face deformity.

Distinct atrophic histological changes occur within the dermis and epidermis. Within the epidermis, the density of keratinocytes and melanocytes declines significantly, creating thinning and abnormal pigmentation of the skin. Langerhans cells, a component of cell-mediated immunity, likewise decrease. Within the dermis, elastic fibres begin to disappear, creating a deficiency in tissue recoil that manifests as excess wrinkling, and there is also a significant decrease in collagen and ground substance. Retraction of dermal papillae and rete ridges causes flattening of the dermal–epidermal junction. In combination, these changes result in the decreased capacity to retain moisture, creating the dryness that typifies aged skin.[15]

Atrophy of subcutaneous fat is another hallmark of facial ageing. The supporting fascial attachments around the fat pads begin to weaken with age. Gravitational forces gradually redistribute these tissues in a more inferior and lateral direction. Consequently, entire subunits, such as the malar fat pad and jowl, become ptotic and contribute to a tired facial appearance.[16–20]

Continuous remodelling of the facial skeleton leads to volume loss with increased age.[20–22] Relative changes can be seen in terms of both volume reduction and expansion. An appreciable reduction in height occurs with modest increases in width and depth. For example, the vertical height of the maxilla decreases while the width of the orbital bones increases. Such changes lead to a disproportionate balance between the available bony surface area and soft-tissue coverage. This process further contributes to inferior displacement of the cheek pad and skin. This same process accounts for jowl formation and sagging along the neckline.

Extrinsic mechanisms of ageing most commonly involve skin damage sustained from solar exposure, known as photoageing. Ultraviolet radiation is well known to contribute to actinic damage through direct or indirect DNA damage. Whereas intrinsic ageing of the skin uniformly results in atrophy of the tissue, actinic changes tend to lead to thickening. In addition, photoageing causes disorganization of dermal elastic tissue fibres, termed elastosis, which contributes to further development of fine skin wrinkles and is a hallmark of the photoageing process.[23]

CLINICAL EVALUATION

Achieving success in ageing face surgery begins with proper patient selection. One of the most critical factors to consider is the patient's psychological motivation for surgery. Multiple studies[24, 25] demonstrate that patient psychology is a significant determinant of post-operative satisfaction in ageing face surgery. The patient who has a stable self-image and internal desire for a more youthful appearance is more likely to be satisfied with the post-operative result. In contrast, the patient seeking surgery to remedy a situational or social dilemma may have unrealistic expectations. This situation often heralds unhappy results.

It is imperative the patient and surgeon are in complete agreement on the indications for surgery and the resulting anticipated changes. Rhytidectomy is an excellent technique to correct visible signs of ageing in the lower two-thirds of the face and upper neck. This includes redundant facial skin and deep rhytids, jowling or loss of a well-defined mandibular contour, and modest improvement of prominent nasolabial folds. Patients should be counselled that rhytidectomy is not effective for superficial rhytids resulting from solar damage or minor depressions secondary to acne scarring. These abnormalities are more appropriately treated with adjunctive techniques, such as laser resurfacing or dermabrasion.

As with any elective procedure, overall good health is a prerequisite in ageing face surgery. Pre-operative evaluation includes a thorough history and review of systems to screen for potential complicating factors. Many patients consider rhytidectomy following significant weight loss. If further weight loss is planned or a history of repeated weight loss and gain is suspected, surgery should be delayed until a plateau is reached. Patients with a history of coronary artery disease, hypertension, pulmonary compromise and hepatic or renal insufficiency should be cleared by the appropriate medical specialist in advance. Relative contraindications to rhytidectomy include predisposition to poor wound healing, as seen in diabetes mellitus, chronic steroid use, connective tissue disorders (such as Ehlers–Danlos syndrome) and past radiation therapy. An absolute contraindication to surgery is a history of a bleeding diathesis.

All medications containing aspirin and non-steroidal anti-inflammatory agents are discontinued at least 3 weeks prior to surgery to minimize bleeding. It is important to enquire about use of supplemental vitamins (particularly vitamin E) and homeopathic preparations (including *Ginkgo biloba* and garlic). These medications are in widespread use but rarely disclosed voluntarily by patients and can contribute to unexpected bleeding.

A history of tobacco use is particularly relevant in the assessment of the ageing face patient. It has been estimated by Rees and Aston that smokers have a 12 times increased risk of skin slough following rhytidectomy compared with non-smokers.[26] This is attributed to a higher incidence of haematoma formation and vasoconstriction. Although long-term effects of smoking on skin cannot be negated by peri-operative cessation, surgical complications can be reduced by smoking cessation within 2 months of surgery.

There is no ideal age when considering timing for ageing face surgery. Chronological age alone should not be used as the qualifying criterion. More importantly, consideration is given to the visible degree of ageing in a particular individual. Patients demonstrating mild to moderate degrees of ageing are more likely to achieve a natural, rejuvenated appearance. Signs of advanced ageing, such as extreme skin sagging, are more difficult to correct and

will limit expected improvement. Rhytidectomy is often an operation of compromise. Dramatic improvement can be made in one region, but this may occur at the expense of suboptimal change in another. In patients with advanced signs of ageing, it is beneficial to strive for less dramatic but more natural change initially, with further refinement at a later date if necessary.

Physical examination begins with assessment of the patient's skin type. An ideal candidate for rhytidectomy is an individual with fair, medium-thickness skin. Dark patients usually have thicker skin and enjoy less dramatic improvement. The increased weight of their skin also results in more post-operative skin relaxation. The presence of a moderate amount of skin elasticity is beneficial. Less elastic skin can be tightened by rhytidectomy, but the duration of improvement may be less satisfactory. A modest degree of subcutaneous fullness is also desirable, particularly in the midface. This reflects a healthy adipose tissue layer and contributes to a more youthful look. This can be enhanced with the use of complementary fat grafting.

Facial skeletal structure can help predict a more or less favourable surgical outcome. Patients with a strong facial skeleton usually demonstrate more obvious improvement. Well-defined bony contours provide excellent support for skin redraping and accentuate desirable facial features. Patients with mid-facial hypoplasia are poor candidates for rhytidectomy alone and typically require adjunctive procedures. Similarly, patients with microgenia and poor chin definition require chin augmentation in conjunction with rhytidectomy to achieve enhanced results.

Many facelift patients express concern regarding skin laxity and fullness in the submental region. This is best appreciated on a profile view by assessing the cervicomental angle. The submentum should be palpated to determine relative contributions from redundant skin, fatty tissue and platysmal banding. Redundant skin alone can usually be addressed with standard rhytidectomy technique by suspension of the cervical skin. Excess fatty tissue is most effectively treated by submental liposuction. Patients with prominent platysmal banding require platysmaplasty to attain a more favourable cervicomental angle. In patients with extreme fatty deposition, platysmal banding may not be appreciated until after liposuction has been performed. Thus, patients should be counselled that platysmaplasty may be indicated in addition to submental liposuction. It is worth noting that a subgroup of patients has an inherent anatomic limitation to the degree of improvement that can be realized in the submental region. These patients have an abnormally low positioned hyoid bone and are considered less ideal candidates for surgery. Such patients should be thoroughly counselled that facelift surgery may not significantly affect their submental profile view, even in conjunction with liposuction and platysmaplasty.

Pre-operative photographs are taken with standardized 1:8 full-face frontal, lateral and oblique views. Digital imaging can be useful in demonstrating to the patient realistic changes that may be expected following surgery.

SURGICAL TECHNIQUES

This section outlines general steps in surgical technique for SMAS rhytidectomy, submental liposuction, platysmaplasty and autologous fat injection.

The patient is marked pre-operatively in the sitting upright position. Areas of special concern are highlighted, as well as anatomical landmarks such as the geniomandibular groove, mandibular border and submental triangle. A pre-operative intravenous dose of an appropriate anti-staphylococcal antibiotic is then administered.

We prefer to perform rhytidectomy under general anaesthesia, but local anaesthesia with intravenous sedation is well tolerated by the patient. Anaesthetic solution containing 1:100 000 epinephrine is infiltrated along the pre- and postauricular borders and in a fan-like fashion beneath the facial and upper cervical skin flaps. If the neck is to be addressed by either liposuction or platysmaplasty, local anaesthetic is additionally infiltrated throughout the submental region. The endotracheal tube is prepped into the surgical field and positioned to allow side-to-side movement during the operation. The entire face, neck and scalp are prepped and draped in sterile fashion.

Careful incision design and placement are vital to achieving natural-appearing results in rhytidectomy. The ideal incision camouflages scar formation, minimizes changes in the temporal and postauricular hairline and avoids distortion of the earlobe. An oblique incision begins in the temporal hair tuft region and varies for the individual patient. If a low temporal hairline is present, the incision is placed within the hair tuft to raise the hairline to a normal position post-operatively. If a normal or elevated temporal hairline is present, the incision is designed to run directly on the hairline to avoid elevating it further. The incision extends posteriorly 2–3 cm, gently curving into the temporal hair. It is then redirected inferiorly toward the root of the helix and into the preauricular crease.

A post-tragal incision is used in most female patients. The incision is positioned 2–3 mm onto the posterior tragal surface and not deep toward its base. It exits at the inferior margin of the tragus and transitions toward the lobule. Alternatively, a pre-tragal incision can be used that courses within the preauricular skin crease. In male patients this incision is placed approximately 1 cm anterior to the preauricular crease to avoid advancing hair-bearing skin too close to the auricle.

The lobule incision can be transposed according to individual need. In patients with a 'hanging lobule', the incision can be placed 1–2 mm below the lobule attachment and readily camouflaged. If a dependent lobule is not present, the incision is made at the junction of the lobule and infra-auricular skin. The lobule incision extends onto the posterior surface of the auricle coursing over the conchal bowl. Approximately 3–5 mm should remain between the incision and the postauricular sulcus. In the male patient, the incision rests within the sulcus to avoid displacing hair-bearing skin onto the ear. The incision extends to the level of the fossa triangularis before turning posteriorly. A less dependent skin flap can be created in patients with a smoking history by limiting the superior extent of this incision.

A V-shaped dart is created as the incision traverses the sulcus and minimizes post-operative webbing. The incision extends into the hair-bearing skin before coursing parallel to the occipital hairline (**Figure 88.1**).

Elevation of the skin flap begins in the postauricular region. The flap is elevated in an avascular plane while preserving the subdermal plexus and thin fatty layer on the undersurface of the skin. Elevation continues into the neck in a supraplatysmal plane. The preauricular skin flap is elevated in a similar manner. Near the zygomatic arch, dissection is limited to the posterior one-third of the arch to avoid potential frontal nerve injury. A full-thickness skin flap is elevated off the tragal cartilage. This facilitates redraping of the skin and helps maintain the natural tragal contour. The preauricular skin flap is elevated approximately 9 cm anteriorly and can be extended over the jawline into the neck. Dissection in the neck is most commonly performed in the subcutaneous plane. In many patients, liposuction of the neck can be performed without connecting the preauricular with the neck dissection.

Once the skin flap is elevated, the SMAS is identified. A horizontal incision is made in the SMAS just below and parallel to the zygomatic arch but limited to the posterior one-third segment. This connects to a vertical limb coursing 2 cm anterior to the tragus. The SMAS incision should not extend beyond the angle of the mandible because the marginal mandibular nerve is in close proximity. The SMAS flap is elevated approximately 3–5 cm (**Figure 88.2**). In many cases the platysma is incorporated as an extension of the SMAS. The SMAS flap is then advanced and primarily pulled in a superior vector with a slight posterior vector. Maximal pull should be avoided when suspending the first side as this may restrict mobility of the contralateral side and result in facial asymmetry. A triangular segment of SMAS is excised and the edges of the SMAS flap are then sutured to the dense fibrous tissue at the inferior margin of the zygomatic arch and the preauricular SMAS. Multiple 4-0 PDS and 5-0 nylon sutures can be used for this SMAS imbrication. In some patients, a postauricular SMAS flap can be dissected and suture plicated to the mastoid periosteum (**Figure 88.3**).

After tightening the SMAS, the skin flap advances easily over the face. The postauricular skin is pulled superiorly and slightly anteriorly, whereas the preauricular skin is pulled superiorly and slightly posteriorly. The postauricular skin is temporarily anchored at its superior margin with staples. Similarly, the superior margin of the preauricular skin is anchored to the temporal hairline. After careful

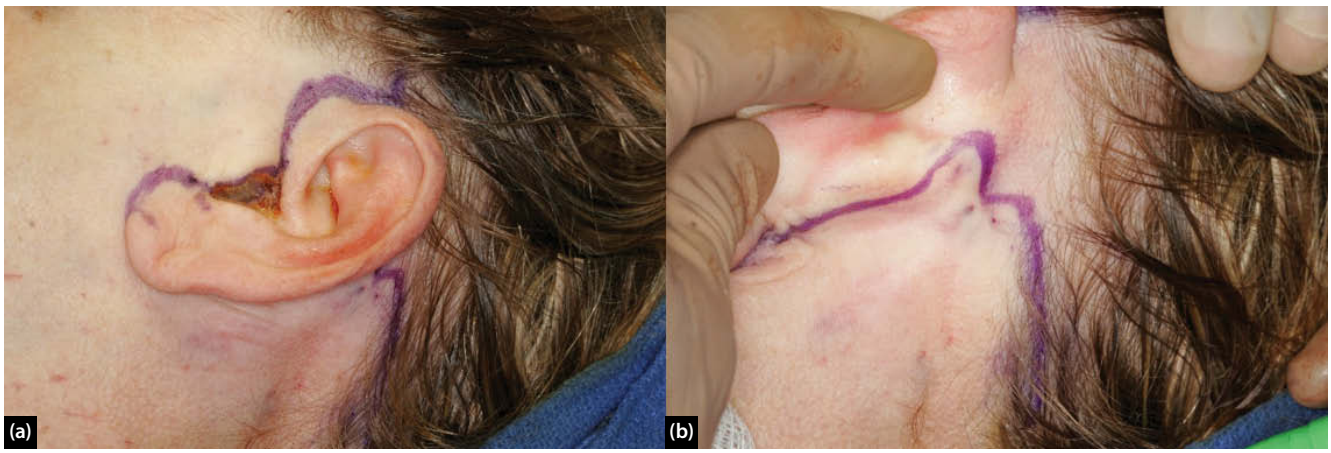

Figure 88.1 The post-tragal incision is placed just behind the tragal cartilage (a). Note how the outline of the tragus is defined by the incision. The postauricular incision **(b)** runs along the posterior surface of the conchal cartilage with a V-shaped dart in the posterior limb of the incision as it moves toward the hairline. This acts to break up the scar and prevent contracture.

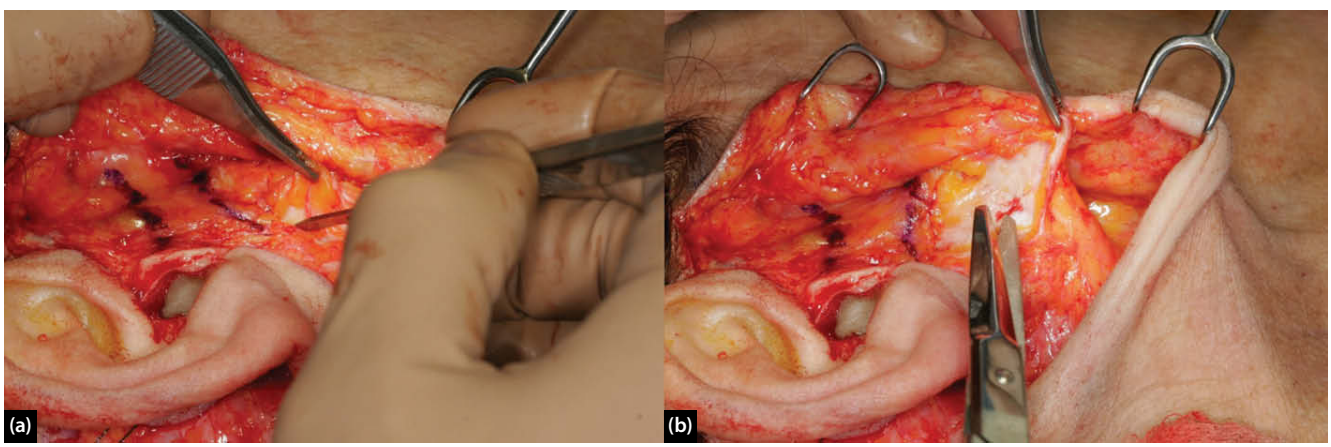

Figure 88.2 The SMAS is incised after elevation of a subcutaneous flap (a). A sub-SMAS flap is carefully elevated from below the zygomatic arch extending anteriorly and inferiorly **(b)**.

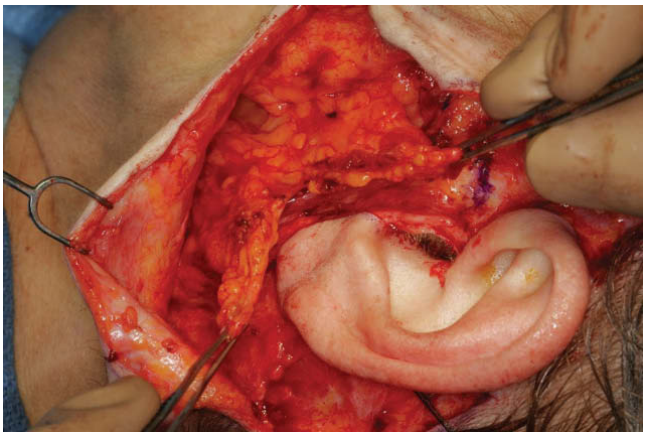

Figure 88.3 The SMAS flap is advanced superiorly and slightly posteriorly. In this case the flap was bifurcated and separately suspended to the preauricular SMAS below the zygoma, and to the mastoid periosteum.

measurement, the excess skin is sharply trimmed. The tragal skin flap should be thinned sufficiently to allow natural redraping over the cartilage. It is imperative to avoid excess skin tension as displacement of the tragus can easily result. Meticulous care should be taken to realign the occipital and temporal hairline.

Attention is then focused on the portion of the skin flap hammocking the lobule. The skin is sharply divided to 'release' the lobule, leaving a significant hammock effect on the lobule. This support on the lobule will help prevent a satyr ear deformity due to post-operative settling of the earlobe. The excess skin is trimmed to recreate a natural lobule contour. It is important to minimize tension placed on this closure.

The entire incision is closed in a layered fashion over a ¼-inch Penrose or suction drain. The subcutaneous layer is closed with 5-0 polydioxanone sutures. The temporal, preauricular and lobule skin segments are closed with 6-0 nylon vertical mattress sutures. The postauricular skin is closed with 5-0 fast-absorbing plain gut suture. Antibacterial ointment is applied to all incision lines followed by a dry gauze pressure dressing.

All rhytidectomy patients are observed overnight. The following morning, the drain is removed and a pressure dressing is reapplied. Antibiotics are prescribed for a total of 10 days post-operatively. Sutures are removed 7–10 days after surgery. Oedema resolves over several weeks and facial contour stabilizes at approximately 4–6 weeks after surgery. Erythema of the tragal incision should fade over several months (**Figure 88.4**).

SUBMENTAL LIPOSUCTION AND PLATYSMAPLASTY

When indicated, submental liposuction and platysmaplasty are performed prior to the rhytidectomy. A midline incision is made within the first well-developed submental crease posterior to the mandible. If liposuction alone is planned, this is limited to a 5 mm stab incision. If a wider incision is later needed for platysmaplasty, the stab incision should be made initially to maintain vacuum pressure during liposuction.

A wide variety of liposuction cannulas exists, ranging from flat to round-tipped with an array of suction port designs. Surface irregularities appear to be minimized with the use of smaller cannulas. We prefer pre-tunnelling with a 2 mm cannula followed by applied low suction. The cannula is inserted into the subcutaneous space between the dermis and platysma. The dominant hand controls movement of the cannula while the contralateral hand guides tip position. Pre-tunnelling involves limited dissection to facilitate passage of the larger cannula. Liposuction is performed by dissecting with the cannula in radial fashion away from the incision. One atmosphere (760 mmHg) of negative pressure is usually sufficient. The suction port should always be directed away from the skin to minimize dermal trauma and dimpling. Uniform suctioning is performed across the submental triangle down to the hyoid bone. Liposuction should be limited near the inferior border of the mandible to avoid injuring the marginal mandibular branch of the facial nerve. Periodic inspection of the skin using the 'pinch and roll' technique helps determine the degree and extent of liposuction required. A sufficient amount of fat should remain to preserve natural skin cushioning.

Platymasplasty requires creation of a slightly wider submental incision. Blunt scissor dissection is used to expose the medial border of the platysma muscles. Residual fat surrounding the incision and between the muscles is removed under direct vision. If minor platysmal banding is present, plication of the exposed muscle borders across a short distance is sufficient to improve the submental contour. In patients with severe platysmal banding, both muscles are horizontally incised at the level of the hyoid bone. The muscles are then plicated anterior to this incision, thereby recreating a well-defined cervicomental angle. The submental incision is closed in a layered fashion.

AUTOLOGOUS FAT TRANSFER

The patient is marked in the pre-operative holding area in an upright position with the patient in neutral gaze. Areas of volume deficiency are carefully noted. These typically include the nasojugal, submalar, malar, nasolabial and geniobuccal regions. Marionette lines and prejowl sulci can be filled to restore a more youthful shape. The submental crease can be augmented to ease the transition to a ptotic chin. Areas of concern are addressed based on extensive pre-operative discussion with the patient with the aid of digital photographs. Potential donor sites are examined. The most easily accessed harvest sites during an aesthetic facial surgery are those that do not require significant patient repositioning, including the abdomen, flanks and lateral thighs. The medial thigh is a potentially robust donor site but requires minor repositioning to a frog leg position to facilitate harvest. Quite frequently, autologous fat grafting is undertaken in conjunction with other

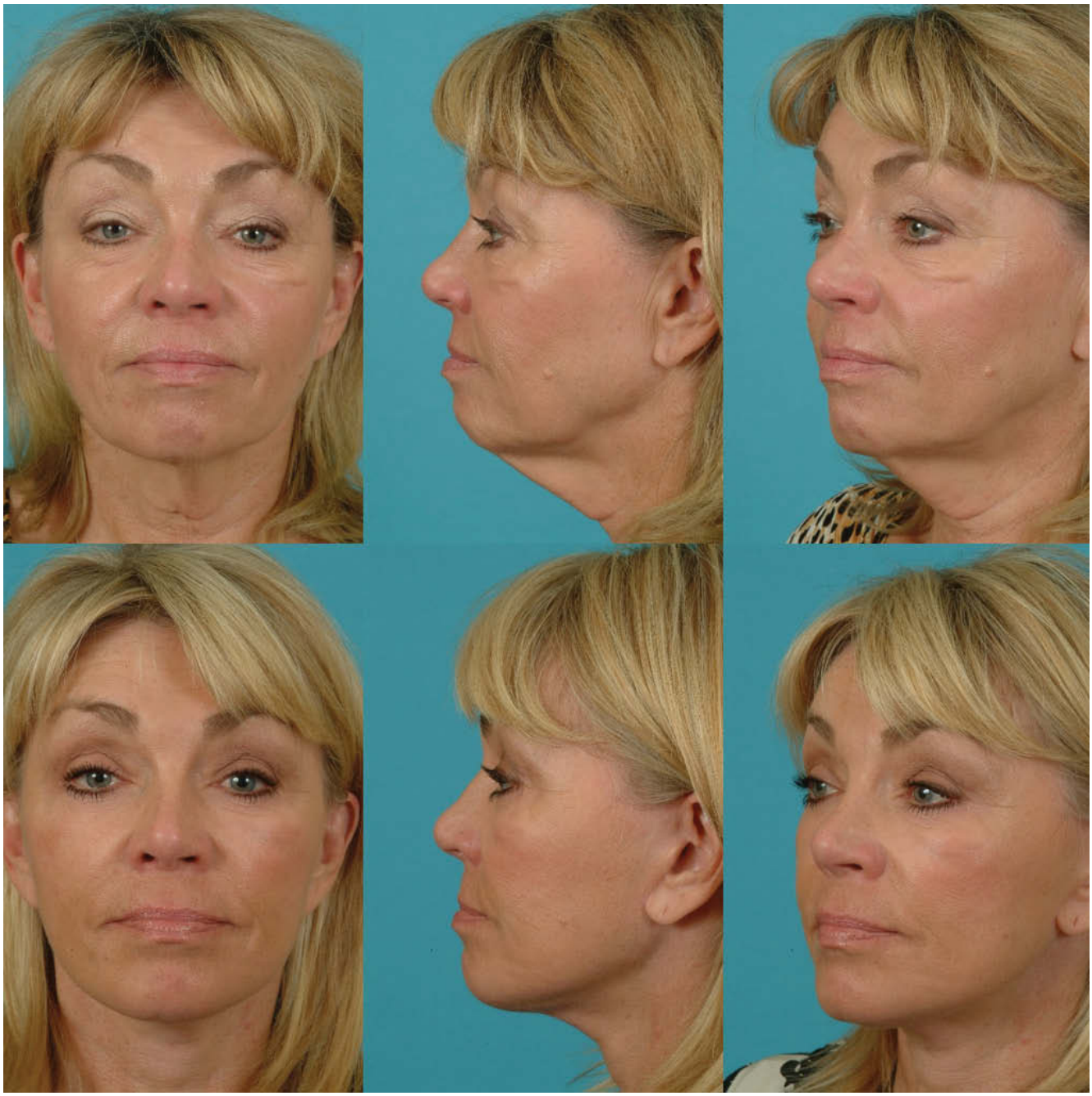

Figure 88.4 Patient treated by SMAS imbrication rhytidectomy with upper and lower lid blepharoplasty, submental liposuction, platysmaplasty and chin augmentation. Pre-operative views (top row). Post-operative views (bottom row).

aesthetic facial surgery to achieve an optimal result. Thus, it is most aptly considered a complementary procedure.

We usually undertake fat grafting as part of an extended procedure requiring general anaesthetic. However, fat grafting can be performed under the spectrum of anaesthetic options. During surgery, the donor sites are prepped into the sterile field. A small aliquot of local anaesthetic is infiltrated subcutaneously at the site of planned incisions. A 11 blade scalpel is used to create a 3 mm stab incision at the site of planned harvest. Incisions within the umbilicus are placed within a natural skin fold if present.

A tumescent liposuction technique is used to harvest the fat for transfer. Tumescent solution containing 20 mL of 1% lidocaine and 1 amp of epinephrine in 1 L of isotonic saline is infiltrated into the subcutaneous fat plane using a blunt-tip cannula. The tumescent solution is permitted to stand for a period of time prior to liposuction to allow for adequate vasoconstriction. Fat is then harvested using a liposuction technique similar to that described above. A 2–3 mm blunt multihole cheese grater type cannula is preferred for the harvest. Careful attention is paid to the plane of harvest to avoid irregular scarring of the dermis or entry into the abdominal cavity. The non-dominant hand continuously palpates the depth of the cannula and controls its movement. The amount of fat required for facial injections is typically well below the volume

performed in a standard liposuction procedure, which decreases the morbidity of the technique substantially. Patients should be counselled not to expect a significant aesthetic improvement at the donor site.

Once the fat is harvested, it is transferred from the suction cannister and placed in 10 mL Leuer-lock syringes. These syringes are capped and placed in a centrifuge in sterile sleeves and spun at 3000 rpm for 3 minutes. The infranatant is drained away and the fat is placed in 1 mL tuberculin syringes for injection.

For introduction of the injection cannula, 3 mm stab incisions are created with a 11 blade scalpel. A typical injection can be accomplished through three such incisions on each side, in the submalar region, the base of the nasolabial fold and the peak of the geniobuccal sulcus adjacent to the corner of the mouth. Additional incisions can be placed as needed. The premarked regions are then carefully injected with fat using a blunt 20 G injection cannula (**Figure 88.5**). Constant controlled motion and attention to the depth of injection help prevent irregularities. Microaliquots of fat are carefully deposited in multiple tissue planes. The volume is determined by the degree of deficiency and the patient's goals for rejuvenation. Special attention is paid to the depth of injection in the nasojugal region and along the orbital rim, where thin skin is very unforgiving of irregularities. The non-dominant hand protects the orbit during injections of the upper midface near the eyelid–cheek junction. When completed, the incisions can be closed with a single fast-absorbing gut suture. **Figure 88.6** shows pre- and post-operative photographs of a patient who underwent autologous fat grafting using the above technique.

COMPLICATIONS

Haematoma

Haematoma formation is the most common complication of facelift surgery. In most modern series, the incidence of haematoma is reportedly less than 4%.[27] A majority occur within 48 hours post-operatively and often within the initial 6–8 hours. Poor haemostasis, extended skin flaps and severe hypertension have all been purported to be influential factors.[28] Some haematomas are so small they are considered clinically insignificant and can be observed expectantly. Others result in a discrete pooling that should be addressed in a timely manner with aspiration using a large-bore needle. Alternatively, a small stab incision made within a well-developed skin crease will allow adequate drainage. Application of a pressure dressing may help in preventing recurrent formation.

An expanding haematoma is a surgical emergency requiring immediate attention. This is heralded by acute swelling, pain and discolouration along the buccal surface. All surgical dressings must be removed and the skin flaps inspected closely. If flap viability is in question, the immediate removal of consecutive sutures may temporarily restore adequate circulation. Exploration of the wound and evacuation of all visible clot, preferably in the operating room, is mandatory. In a majority of cases, the specific source of bleeding is never identified.[29] Nonetheless, failure to recognize and treat haematoma can result in abnormal pigmentation, alopecia, skin puckering and flap necrosis.

Nerve damage

Nerve damage resulting from rhytidectomy is a rare occurrence. Baker and Conley reported a 0.1% incidence of permanent nerve damage in a series of 6500 rhytidectomies.[30] The most commonly injured branch is the great auricular nerve. Mechanisms of injury include inadvertent dissection deep to the sternocleidomastoid fascia, plication of the postauricular SMAS and transmission of the thermal electrocautery. In most cases, the integrity of the nerve has not been disrupted and full return of sensation can be expected.

Branches of the facial nerve are the most commonly injured motor nerves in rhytidectomy. Proximity to the plane of dissection, especially during elevation of the SMAS, makes them particularly vulnerable to mechanical injury. The frontal nerve is most often injured during SMAS elevation near the zygomatic arch. Within this region, the frontal nerve becomes increasingly superficial as it courses over the middle segment of the arch. If surgical

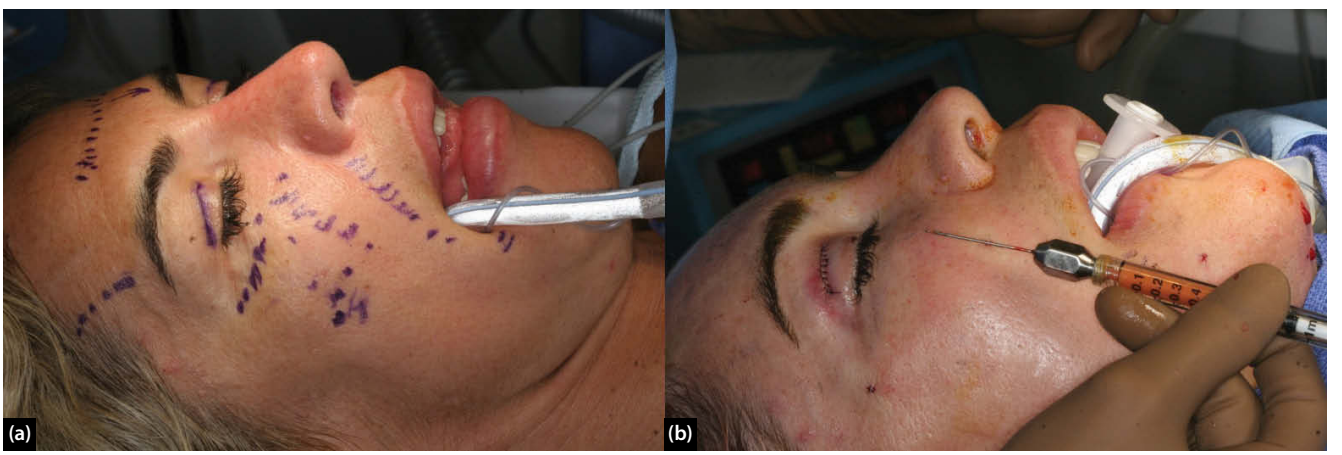

Figure 88.5 Markings for facial fat injection (a left). Intra-operative view during injection procedure **(b right)**. An injection cannula is used for infiltration.

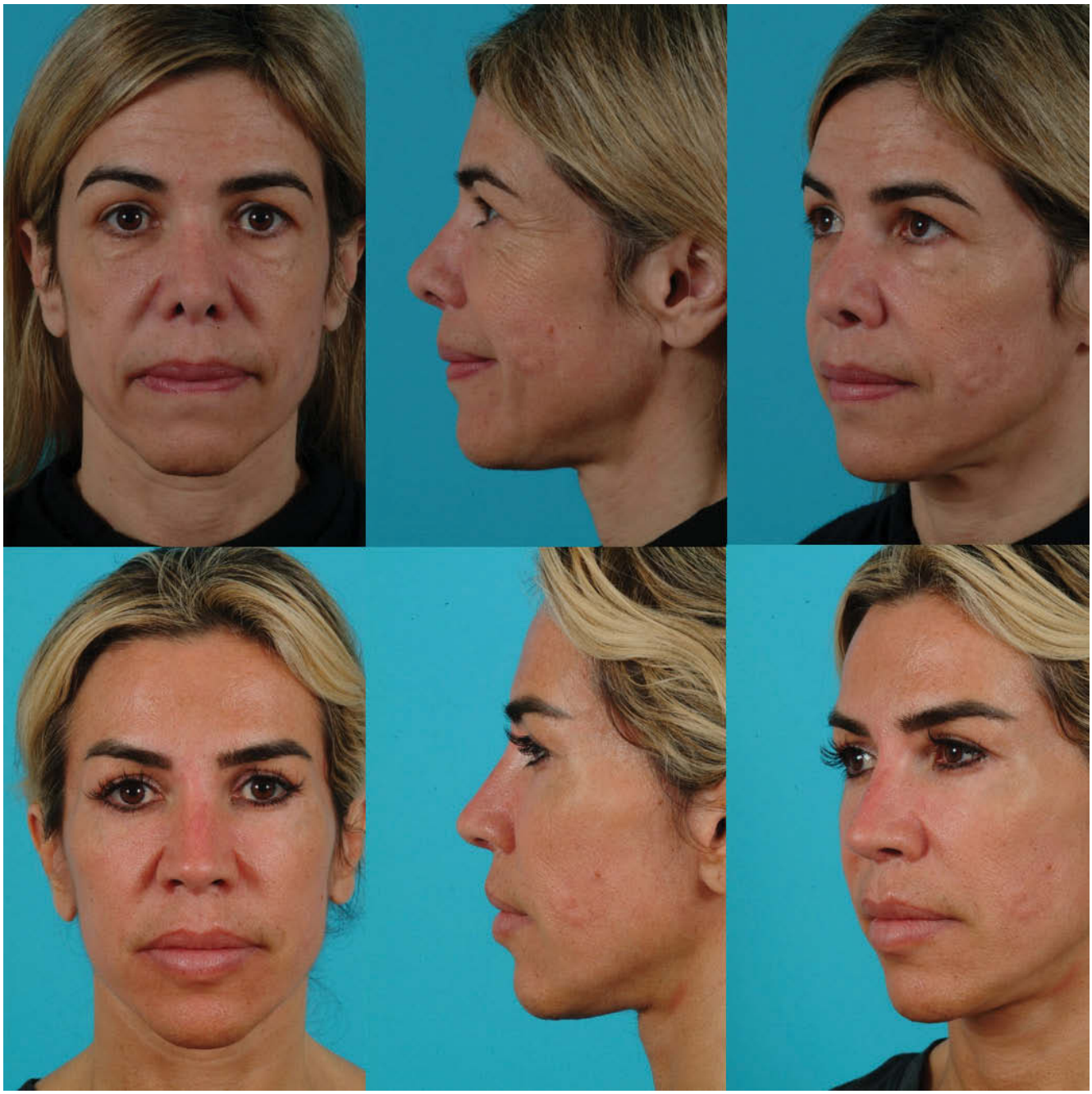

Figure 88.6 Patient treated by facelift, endoscopic browlift and upper blepharoplasty with autologous fat injection. Pre-operative views (top row). Post-operative views (bottom row).

dissection is limited to the posterior one-third of the arch, risk to the frontal nerve branch is virtually negated. Injury to the marginal mandibular nerve typically results from transection of the platysma or excess SMAS retraction near the angle of the mandible. Fortunately, nearly 85% of paralyzed motor branches will recover spontaneously with minimal residual deficits.

Skin slough

Skin slough most commonly arises as a consequence of unrecognized and untreated haematoma. Excess skin tension and disruption of the subdermal plexus are also frequent causes. The toxic effects of smoking have long been recognized as another predisposing factor in skin sloughing.[31] The postauricular flap is at greatest risk because skin tension is typically highest in this region. Dependent flap length is also maximal and the skin is relatively thin along this surface. In general, expectant management with meticulous wound care is the rule for skin sloughing. However, frequent visits and repeated patient reassurance are necessary. Superficial epidermal sloughing typically results in an acceptable appearance after healing. In cases of full-thickness sloughing, eschar formation is

seen and serial debridement is required to promote healing by secondary intention. Invariably, patients with full-thickness loss can expect some degree of hypertrophic scarring and abnormal pigmentation.

Alopecia

Alopecia in the temporal region is a common complication of rhytidectomy and one that is easily avoided with careful incision design and placement. In some cases alopecia is a transient phenomenon, termed telogen effluvium, attributed to temporary follicular shock. In other instances alopecia is more permanent, for example when the hair follicles have been injured by thermal electrocautery. If no evidence of regrowth is noted after a waiting period of 4–6 months, hair restoration can be attempted using either micrografts or local skin flaps.

Satyr ear deformity

Satyr ear, or 'devil's ear' deformity, results from improper incision placement around the lobule and/or overzealous excision of the skin flap. Tension caused by post-operative relaxation of skin leads to an inferior displacement of the lobule and abnormal banding. This complication can be avoided by preserving a tight supporting margin of skin below the lobule attachment that actually pulls up on the lobule.

Complications of fat injection

When performed correctly, fat grafting by injection is a safe technique with few and rarely significant complications. Irregularities of contour are the most frequently encountered complication. These can range from a discrete focal irregularity that can be managed with simple excision, to generalized overcorrection, which is very difficult to manage. Intralesional steroid injection, ultrasound therapy and local massage all represent viable conservative treatment methods of minor focal deformities. The transplanted fat can be susceptible to changes in weight, particularly large amounts of weight gain, which lead to the overcorrection deformity. Pre-operative counselling should clearly address these issues, and a conservative approach to fat grafting is always preferable. Donor site morbidity can include haematoma, infection, bruising and dermal scarring. These can be minimized with careful harvesting technique.

The most serious complication of fat or other filler injection to the face is inadvertent intravascular injection resulting in embolism, which can lead to serious adverse events including blindness, stroke and local tissue ischemia or necrosis.[32] Marked local blanching of the skin is a warning sign and should lead to a heightened degree of suspicion. Immediate actions that can be taken include applying nitropaste locally, performing local massage and placing the patient in the Trendelenburg position.[13] Better still is to practise careful injection technique to minimize this risk, by using blunt-tipped cannulas with initial aspiration, low injection pressures, small volumes per pass, or local epinephrine to induce vasoconstriction. As always, the clinician should develop an injection plan based on a detailed understanding of the underlying facial vascular anatomy.

BEST CLINICAL PRACTICE

- ✓ A post-tragal facelift incision is used in most female patients, while a pretragal incision is used in males.
- ✓ Elevation of the skin flap and SMAS flap should be limited to the posterior one-third of the zygomatic arch to avoid injuring the frontal nerve branch.
- ✓ The postauricular skin flap is suspended superiorly and anteriorly, while the preauricular skin flap is suspended superiorly and posteriorly. It is imperative to avoid excessive tension on any portion of the skin flap.
- ✓ Submental liposuction and/or platysmaplasty should be considered in patients with neck fullness not attributed to excess skin alone.
- ✓ Post-operative haematoma formation requires timely assessment and intervention to minimize chances of a suboptimal aesthetic outcome.
- ✓ Facial fat injections must be performed carefully with proper technique to avoid complications.

FUTURE RESEARCH

- ➤ Advances in rejuvenation of the midface and upper third will allow for more natural surgical rejuvenation.
- ➤ Techniques and applications for fat grafting will continue to expand, particularly as the underlying biology is better understood.

KEY POINTS

- Sun damage to the skin, atrophy of tissues and the effects of gravity bring on the changes seen in the ageing face patient.
- Pre-operative analysis is critical to determine the specific needs of the patient.
- Incision placement is critical to help hide incisions and avoid deformity of the hairline.
- Patients must stop smoking cigarettes 3–4 weeks before surgery to avoid vascular compromise and necrosis of skin flaps.
- Dissection of the SMAS allows correction of jowling over the body of the mandible and neck deformity. Placement of tension on the SMAS plication takes tension off the skin closure.
- The most commonly injured nerve in facelift surgery is the great auricular nerve.
- The incidence of haematoma formation is less than 4%. An expanding haematoma constitutes a surgical emergency.
- Facial fat injection is a valuable adjunct to ageing face surgery, as it directly addresses facial volume deficiency associated with ageing.

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CHAPTER
89

NON-SURGICAL REJUVENATION OF THE AGEING FACE

Lydia Badia, Peter Andrews and Sajjad Rajpar

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SEARCH STRATEGY

Data in this chapter may be updated by a search of PubMed using the keywords: non-surgical face, look younger, hyaluronic acid fillers, collagen stimulation, polycaprolactone, botulinum toxin, botox, retinoids and chemical peels.

INTRODUCTION

Ageing transforms the face to create a look that often does not reflect the vibrant person inside. Maintaining a youthful appearance can have a profound effect on self-esteem and personal and professional relationships; the exponential uptake of facial aesthetic procedures requires no further explanation. In this chapter, an overview of the core non-surgical interventions which are recognized to be safe and effective is provided.

The causes of ageing in relation to facial appearance may be intrinsic or extrinsic. Intrinsic skin ageing is caused by the same genetic pathways that lead to ageing of all the other organs of the body; thin, atrophic, hypopigmented and fragile skin results from a total reduction in cell count and function. Intrinsic ageing of the subcutaneous tissues is also highly relevant as bone resorption, muscle atrophy and variable atrophy and hypertrophy of individual fat compartments leads to ptosis of the soft tissues, sagging, hollowing and rhytids.

Extrinsic skin ageing is caused by lifestyle and environmental factors. Notably, skin ageing is rapidly accelerated from excessive exposure to ultraviolet light and smoking; several observational and twin studies have demonstrated this. Recent evidence suggests that environmental hydrocarbon pollution and infrared light exposure may also be contributory to skin ageing. The results of extrinsic ageing are the presence of increased fine and deep lines from loss of elastin and collagen fibres, solar elastosis from the disorganization of elastin fibres creating a sallow colour tone, hyperpigmentation usually in the form of solar lentigines, and erythema from telangiectasias. These characteristics are often referred to as the signs of 'photoageing'.

It is important to establish the concerns of any patient considering non-surgical treatments. Typically, these are to improve the appearances of fatigue, to appear less angry and negative, and to brighten skin tone and freshness. In general, the desire to appear 'well' and optimum for chronological age, and to maintain this, is a frequent and realistic goal. Looking substantially younger or back to a certain stage in life is perhaps more unrealistic and must be addressed in the pre-procedure consultation.

Broadly speaking, non-surgical treatment modalities may be considered by anatomical layer depending on whether they address changes in the epidermis (e.g. topical treatments and chemical peels), atrophy and inelasticity of the dermis (e.g. topical treatments, chemical peels and fillers), dynamic facial lines caused the pull of the underlying muscles of facial expression (e.g. botulinum toxin injections), and loss of volume at sites of fat or bone resorption (e.g. fillers). Effective facial rejuvenation requires a treatment plan to fit the unique requirements of an individual patient, and providers ought to be familiar with a range of treatment modalities that allow this to be provided. All too often, many doctors, even those who specialize in facial aesthetics, are 'married to one therapy' and this may not be conducive to optimal outcomes.

TOPICAL TREATMENTS AND COSMECEUTICALS

Topical treatments are popular among consumers seeking improvement of cutaneous signs of ageing because of their convenience, low cost and excellent safety profile. While results may be modest, topical treatments often represent a starting point before progressing towards more invasive facial rejuvenation treatments. A myriad of products are available on the market and this causes confusion for consumers and physicians alike. The relative lack of regulatory restrictions on cosmetics has allowed a range of products categorized as 'cosmeceuticals' to flourish. These are cosmetic products which are purported to provide superior benefits to the skin compared to simple cosmetics while not affecting the structure and function of the skin, as this would otherwise classify them as drugs. The level of evidence required by cosmeceuticals falls significantly short of those required by medicinal products. A greater reliance on *in vitro* data, which is often extrapolated to human skin, is frequent for cosmeceuticals. This allows exemption from the heavy regulatory requirements that *in vivo* research may bring about and which may show changes to structure and function of the skin and cause products to be classified as medicinal instead.[1] Somewhat exaggerated claims of efficacy, often based on *in vitro* data alone, are also not uncommon, which further adds to the confusion.

It is unsurprising therefore that consumers often look towards their physician for advice and recommendations. The yield for physicians is also quite high as, aside from providing an opportunity to build a therapeutic relationship with appearance-conscious patients, 40% may go on to use physician-recommended topical products following initial consultation. Of these, one-third will undergo chemical peels and up to one-quarter will undergo facial injectable treatments in the future.[2] Topical treatments may therefore be considered the first rung of the non-surgical rejuvenation ladder. A topical treatment plan is tailored to the individual needs of a patient and may be designed to target one or more indications (**Table 89.1**).

A selection of topical agents, both medicinal and cosmetic, that a facial plastic surgeon may wish to become familiar with are discussed further here. An in-depth assessment of all available agents is outside the scope of this chapter and the reader is referred to the many excellent texts available on the subject.[3] Advice on the avoidance of lifestyle factors which cause accelerated skin ageing and increased perceived age, such as excessive sun or sunbed exposure and smoking,[4] should supplement and underpin a topical rejuvenation plan.

TABLE 89.1 Indications for topical treatments

Concerns	Clinical signs
Ageing	Fine lines, poor skin texture, photodamage, solar elastosis, atrophic skin
Pigmentation	Solar and post-inflammatory pigmentation
Inflammation	Dry skin, redness and sensitivity
Follicular disorders	Acne, rosacea, folliculitis, enlarged pores

Prescription topical products

RETINOIDS

Retinoids are found in medicinal preparations (requiring a prescription) or in milder forms in over-the-counter formulations (**Table 89.2**). Their use for the treatment of acne dates back to 1959. Kligman's seminal studies in the early 1980s first established the role of tretinoin for the reversal of skin ageing.[5] Since then, over 20 randomized studies have shown the benefits of tretinoin in photodamaged skin.[6] Prescription topical retinoids are the most powerful, effective and evidence-based topical anti-ageing product currently available. Consequently, topical retinoids should form the cornerstone of any topical rejuvenation plan.

The profound biological effect of retinoids on the skin results from their direct action on a family of nuclear hormone receptors, the retinoic acid receptors (RARs) and the retinoid X receptors (RXRs). These receptors are found in all cells, though the key targets are keratinocytes and melanocytes in the epidermis and fibroblasts in the dermis. Activation of retinoid receptors leads to a molecular chain of events that changes protein transcription and modifies cellular function. Histologically this leads to epidermal hyperplasia and impaction of the stratum corneum (producing smoother skin with a 'glow'), increased dermal collagen type I, III and VII synthesis, reduced collagen breakdown and normalization of elastic tissue organization (improving coarse wrinkling and crepe-like skin texture), and a reduction in melanin synthesis and transfer of melanosomes to keratinocytes (improving solar pigmentation).[6] Epidermal effects are seen within 6 months of use, while dermal effects may take a year or longer to become apparent. Treatment ought to be continued indefinitely for continued benefit.

A concentration of tretinoin of 0.025% is considered therapeutically effective while minimizing side-effects. Greater concentrations are associated with a higher incidence of cutaneous toxicity including erythema, scaling, pruritus and sensitivity, and may produce only marginal, if any, additional clinical benefit. Side effects may also occur at lower concentrations and are the most important cause of non-compliance. A typical regime involves the application of tretinoin 0.025% once at night. Strategies to minimize side-effects include using small quantities on

TABLE 89.2 Classification of topical retinoids

Availability	Topical retinoid
Prescription	Tretinoin (all-*trans* retinoic acid) Isotretinoin (13-*cis* retinoic acid) Adapalene Tazarotene
Over-the-counter	Retinaldehyde Retino (all-*trans* retinol, Vitamin A) Retinyl ester

alternate nights initially and gradually increasing this to 1–2 g every night, avoiding astringents, scrubs and detergent-based products, and frequently applying a moisturizer throughout the day. The thinner and more sensitive skin of the eyelids and neck is unlikely to tolerate tretinoin 0.025%, even with incremental exposure, and a compromise is to use an over-the-counter retinol-containing product to these areas. More modest effects are expected as retinol is 20 times less strong.[6]

Non-prescription topical products

HYDROXY ACIDS

The variety of compounds that constitute hydroxy acids is summarized in **Table 89.3**. Many of these have naturally occurring sources. The bathing of Egyptians in soured milk (lactic acid) for beautification over two millienia ago is likely the earliest documented evidence of the use of hydroxy acids for aesthetic skin enhancement.

Alpha-hydroxy acids (AHAs) are the most commonly encountered hydroxy acid in aesthetic formulations. When AHA is applied on pathologically scaly skin such as that found in hereditary ichythosis, the thick stratum corneum separates and a normal thickness epidermis results. The opposite occurs when it is regularly applied on atrophic and aged skin where the epidermis is noted to thicken over a period of several months and revert to a normal thickness.[7] Typically, over-the-counter formulations have concentrations of AHA in the range of 10–12% and are used once or twice a day. A 22-week double-blind randomized controlled trial showed superiority of 8% AHA cream over vehicle in improving the signs of photodamage and sallowness to the skin.[8]

Dermal thickness may also increase from the daily application of AHA because of increased deposition of glycosaminoglycans in the dermis.[7] In addition, glycolic acid has been shown to increase fibroblast proliferation and collagen synthesis.[9] Dermal effects are likely only to occur with higher concentrations of AHA (20–25%) which are available in prescription compounded preparations, though a greater incidence of irritant side effects is found. Higher concentrations still (>25%) constitute superficial chemical peels and are applied once, under the supervision of a clinician, and repeated after a period of time.

TABLE 89.3 Classification of hydroxy acids

Hydroxy acid group	Example	Found in
Alpha-hydroxy acid (AHA)	Glycolic	Sugar cane
	Lactic	Sour milk
	Mandelic	Bitter almond
	Citric	Lemon, orange
Beta-hydroxy acid (BHA)	Beta-hydroxybutanoic	Urine
Polyhydroxy acid (PHA)	Gluconic	Skin
	Gluconolactone	Skin
Aldobionic acid	Lactobionic	Lactose from milk
	Maltobionic	Maltose from starch
Aromatic hydroxyl acid	Salicylic	Winter green leaves

VITAMINS

The concept that vitamins may have a beneficial effect on the skin is very easy to grasp by patients, and additional topical vitamins may easily be introduced after establishing patients on a topical retinoid ('vitamin A cream').

Vitamin B3 (nicotinamide)

Nicotinamide (niacinamide) is the active form of vitamin B3 and is a precursor to a family of enzyme cofactors integral to cellular metabolism. In addition, nicotinamide inhibits poly (ADP-ribose) polymerase-1 (PARP-1).[10] When taken orally at a dose of 500 mg twice a day for 12 months, nicotinamide reduces the incidence of actinic keratosis, basal cell carcinoma and squamous cell carcinoma in individuals who have previously had non-melanoma skin cancer.[11] A 4% nicotinamide gel is available over the counter in the UK and has been shown to be effective for acne,[12] while 2% nicotinamide cream applied to the face for 4–6 weeks reduces sebum production, and improves facial shine and oiliness.[13] A split face study reported that 5% nicotinamide cream applied twice daily for 12 weeks improved fine lines and wrinkles, hyperpigmented spots, red blotches and sallowness while also improving skin elasticity.[14]

Vitamin C (ascorbic acid)

Vitamin C is a potent antioxidant and a cofactor in the collagen synthesis pathway. It may also inhibit tyrosinase and so prevent excessive melanin production, and improve hyperpigmentation. Topically, it is available in concentrations of 5–20%. A 5% cream applied for 6 months to the lower neck and arms of 20 women aged 51–59 years led to significant improvements in the visible signs of ageing though skin biopsy did not show altered levels of collagen.[15] A 23.8% preparation applied for 2 weeks improved several parameters including roughness, fine lines and hyperpigmentation without any significant side effects.[16] A 15% vitamin C may be more stable when combined with 0.5% ferulic acid, a plant-based antioxidant, and together with 1% vitamin E, this triple combination formulation doubles the dose of ultraviolet light required to cause sunburn.[17]

BOTANICAL PRODUCTS

Several hundred botanical remedies for skin disorders exist. There is a perception among the public that botanical products are safe, 'natural' and effective purely by virtue of their origin. The lack of high-quality clinical data makes it difficult to place the utility of botanical compounds into the context of day-to-day clinical practice. A selection of commonly found botanical compounds is included in **Table 89.4**. This list is by no means exhaustive.

TABLE 89.4 A selection of botanical ingredients found in topical preparations and their purported effects

Botanical ingredient	Effect(s)
Aloe	Antioxidant, anti-inflammatory
Arbutin	Skin lightening
Caffeine	Anti-ageing
Co-enzyme Q10	Antioxidant, anti-ageing, skin lightening
Green tea	Antioxidant, anti-inflammatory, anti-ageing, skin lightening
Kojic acid	Skin lightening
Lycopene	Antioxidant, anti-ageing
Polypodium leucotomas extract	Antioxidant, anti-inflammatory
Soy	Antioxidant, skin lightening

In summary, topical treatments are the least invasive of all cosmetic interventions, and providing these may facilitate the engagement of patients who are initially hesitant to have injectable or other more invasive treatments. The physician is under an ethical obligation to recommend products which are effective and in the best interests of the patient.

CHEMICAL PEELS

Chemical peeling is the topical application of chemical agents to cause controlled destruction of part or all of the epidermis, with or without the dermis. This leads to desquamation, liquefaction and coagulation of the affected layers, followed by inflammation, and finally regeneration of epidermal and dermal tissues.

Indications for chemical peeling include fine lines and wrinkles, pigmentation disorders such as solar lentigines and melasma, superficial acne scars and benign epidermal growths. Peels can be classified according to the chemical compounds used or the depth of chemical injury that is produced. Results, recovery time and complication rates vary according to the depth of peel.

Superficial chemical peels are limited to the epidermis and are popular among patients as they are effective while carrying low costs, low complication rates and minimal downtime. Safety in all skin phototypes has been established and recovery within 1–3 days is expected. Superficial peels can be performed with various compounds including trichloracetic acid (TCA) at concentrations of 15% and under, alpha hydroxy acids such as lactic and glycolic acid, and Jessner's solution (14% lactic acid, 14% resorcinol and 14% salicylic acid).

Alpha hydroxy acids, in particular glycolic acid (GA), are commonly used superficial chemical peeling agents. GA peels in concentration ranging from 20% to 70% have been shown to be effective in reducing facial hyperpigmentation and fine lines/wrinkles.[18] Salicylic acid peels have a similar profile, and may be more beneficial for acne-prone skin.[19]

Superficial peels are delivered at 2–4-weekly intervals (typically by an aesthetician), and patients frequently report smoother skin which 'glows', as well as tighter pores and fewer inflammatory acne lesions. Patients often 'feel' the results. Lightening or disappearance of solar lentigines and melasma is also possible. As the target of superficial chemical peels is the epidermis, true dermal changes are minimal (if any) and no number of superficial chemical peels can equate to the skin tightening and improvement in rhytids that a single, correctly performed medium-depth chemical peel may achieve.

Medium-depth peels produce chemical injury to the level of the papillary dermis or the very highest part of the reticular dermis. Due to their depth of penetration, medium-depth peels can produce tissue tightening and an improvement in lines and wrinkles produced by an increase in collagen production and reorganization of elastic bundles. The typical agent used for medium-depth chemical peeling is TCA at concentrations over 30%. TCA is a crystalline inorganic compound which causes coagulative necrosis through extensive protein denaturation. The degree of necrosis varies with the concentration of solution applied.

Monotherapy with 50% TCA may penetrate to the desired depth but carries a high incidence of scarring and should be avoided. A better strategy is to pretreat the skin with Jessner's solution, GA or carbon dioxide slush, to make the epidermis more permeable, and subsequently apply 30–35% TCA. This strategy reduces the risk of scarring from TCA substantially, though pigmentary changes are frequent in darker skin types and medium-depth chemical peels are best reserved of skin phototypes I–III. The reader is referred to an excellent review article on medium-depth TCA peeling by Herbig et al.[20]

BOTULINUM TOXIN

'Botox' has been the most revolutionary anti-ageing treatment in recent years. Doctors Jean and Alastair Carruthers noticed that, when they used botulinum toxin to treat patients with ocular spasms, the wrinkles around the eye disappeared. These results encouraged doctors to treat lines of facial expression such as frown lines, horizontal forehead lines, periorbital lines, nasal lines, perioral lines and platysmal bands.

Botulinum toxin type A (BTX-A) is produced by *Clostridium botulinum*. Synthesized as a single-chain polypeptide of ~150 kDa, BTX has relatively little potency until it is cleaved by trypsin or bacterial enzymes into two chains, a heavy chain of 100 kDa responsible for binding to the target structure and a light chain of 50 kDa known as the toxifying chain. These two chains are linked together by a disulfide bond. The light chain contains a Zn^{2+}-binding motif with enzymatic activity. BTX-A is a zinc-dependent endopeptidase.

When BTX is injected into a muscle, the heavy chain of the molecule binds to glycoproteins expressed specifically on cholinergic nerve endings. After internalization of the whole molecule by pinocytosis, the chains are cleaved within the cytoplasm. The light chain binds with high specificity to the soluble N-ethylmaleimide-sensitive

fusion (SNARE) attachment protein receptors essential for exocytosis of acetylcholine. BTX-A cleaves plasma membrane synaptosome associated protein (SNAP-25) that results in a blockade of vesicle fusion.[21]

Around 2–5 days after BTX is injected into a muscle, paresis occurs, which lasts for at least 3 months and gradually starts to wear off. When the muscle relaxes, it stops pulling on the skin and the wrinkle caused by the muscle pull fades away. The objective duration of action in a given patient seems to be stable, but there is a great variability between different people. Even very low doses produce some effect. By increasing the doses, a plateau is reached where further dose increases will not result in stronger effects. Dose-duration correlations exist to a lesser extent.

On the European market, three different branches of BTX-A are officially registered: Botox®/Vistabel® (Allergan), Dysport® (Ipsen)/Azzalure® (Galderma) and Xeomin®/Bocouture® (Merz). The units are not directly comparable. The products have different amounts of complexing proteins or are free of complexing proteins (i.e. Xeomin®/Bocouture®). The diffusion of the different drugs seems to be dependent on concentration. BTX-A has an excellent safety profile and has been used extensively for facial rejuvenation with a focus on hyperkinetic wrinkles and to improve facial wound healing after surgery.

Botulinum toxin for facial dysfunction and palsy

Similar techniques can also be employed for the dysfunctional paralyzed face so as to improve facial symmetry or in the scarred face to improve dermal contour with the use of fillers. Although facial reanimation surgery primarily relies on dynamic reconstructive techniques,[22, 23] it also draws upon adjunct techniques, such as botulinum toxin, which further augments a positive outcome. In our facial function clinic, BTX is used in a number of situations, primarily in the treatment of synkinesis and also to weaken the non-paralyzed side so as to improve symmetry. As can be seen in **Figure 89.1** botulinum toxin plays a large role in the treatment armamentarium of our facial function clinic and is used in nearly 50% of our patients. As a result, we now run two clinics simultaneously within the facial function clinic allowing the botulinum toxin treatment clinic to run parallel.

Acute facial palsy is the most frequent cranial nerve impairment encountered by otolaryngologists, often presenting as an acute idiopathic facial palsy or Bell's palsy as it is commonly known. Current evidence suggests that 71% of Bell's palsies recover completely and 29% do not. Of those reaching a full recovery, 85% do so within 3 weeks. In Peitersen's study contracture and synkinesis were seen in 17% and 16% of the patient cohort respectively.[24] Synkinesis refers to the abnormal involuntary facial movement that occurs with voluntary movement of a different facial muscle group. The pathophysiological basis of facial synkinesis is likely to be multifactorial although the predominant mechanism appears to be aberrant regeneration of facial nerve fibres to the facial muscle groups. Considering the facial nerve contains approximately 10 000 nerve fibres of which 7000 are motor and the remaining are a combination of parasympathetic efferents and sensory afferents, there is little wonder that disorganization can occur.

The preparation of botulinum toxin in the facial palsy clinic includes 500 units of Dysport which is made up to 5 mL of normal saline; this gives 10 units per 0.1 mL concentration. The Dysport is injected at an angle of 45 degrees using a 1 mL insulin syringe. Local anaesthetic

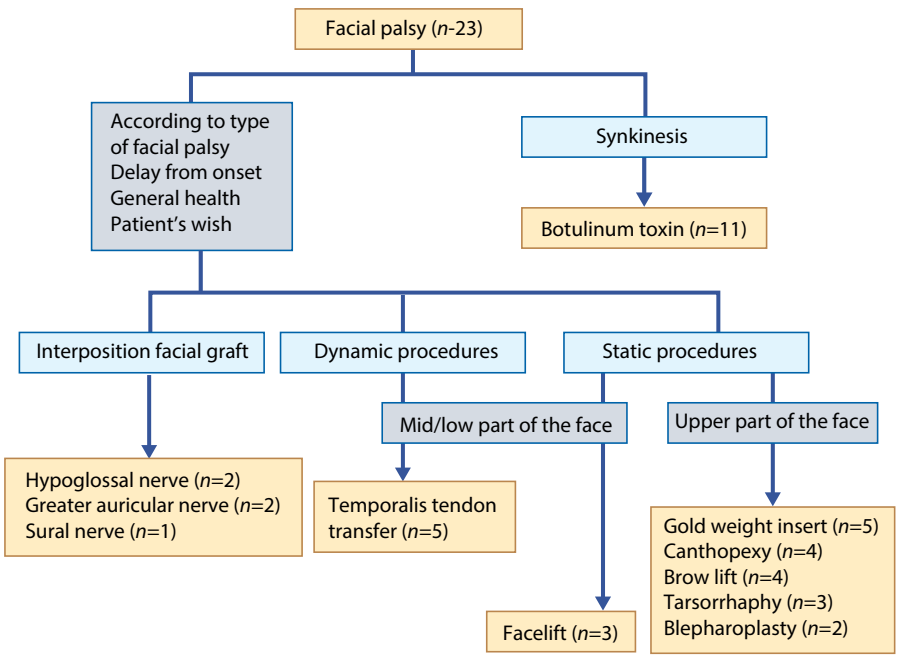

Figure 89.1 Synopsis of facial function treatments.

is not routinely used. In cases of synkinesis, an initial dose of 10 units is used at multiple points within the synkinetic muscle and, in our practice, botulinum toxin is judicially used on the first occasion and then adjusted at 6 months depending on response. We recommend caution when injecting around the orbicularis oculi muscle so as to avoid ptosis and double vision.

As well as for synkinesis we use botulinum toxin for facial contractures following Bell's palsy in particular. These patients can present with disfiguring and painful contractures which come on when stressed or talking, whereby the hemiface goes into contortion. In addition to reducing the contracture, it also helps with the pain. We also employ botulinum toxin in the unaffected overexaggerated side so as to improve symmetry. In a study looking at the use of botulinum injection on the unaffected side of a paralyzed face, the lower muscles of facial expression were injected. The aim of this technique was to reduce the unopposed action of the normal side. The average dose used was 30 units and the affects were first observed at 6 days and lasted up to 4 months.[25]

Botulinum toxin for facial rejuvenation

Temporary chemodenervation of facial muscles responsible for lines and furrows is a well-accepted practice. The commercially available products need to be diluted with 0.9% non-preserved sterile isotonic sodium chloride (saline solution). High dilutions have several disadvantages: more volume needs to be injected, which adds swelling and bruising, less precision as there is more chance of diffusion to adjacent muscles and shorter duration of action. After an informed consent is obtained, the dynamic facial lines are evaluated and standard photographs taken for the purpose of comparison after treatment. The medical history should include any pre-existing facial weakness. Botulinum toxin is contraindicated in patients with underlying neuromuscular junction disorder, allergy to any of its components (human albumin, botulinum toxin), pregnancy and breastfeeding. Aminoglycoside antibiotics and calcium channel blockers may potentiate the effect of the toxin and concomitant use is therefore not recommended.

A regional approach to injection of botulinum toxin facilitates the development of guidelines and injection doses. Total doses should be recorded. Injection of glabellar creases targets the procerus and corrugator muscles, which contribute to dynamic interbrow vertical lines. Asking the patient to frown is the best method for accurately delineating the span of the muscles. The frontalis muscle elevates the brows and creates the horizontal forehead lines. By avoiding the lateral forehead we avoid brow ptosis and a very rigid forehead. However, in patients with an overactive frontalis in the temporal region, undesirable brow arching or 'cocked' eyebrow may occur.

Periorbital lines or crow's feet are produced by the orbicularis oculi muscle, which has a sphincteric action and is responsible for squeezing the eyelids together. This circumferential muscle has three parts: the lacrimal portion assists in tear flow, the palpebral portion passes into the eyelid superficial to the orbital septum and the orbital portion is over the bony aspect and beyond. The lateral and superior aspect of this muscle causes brow depression so, when this downward pull is released, there will be a temporal brow lift. Unlike in glabellar and forehead lines where the injection was deep into the body of the muscle, the injection into orbicularis oculi needs to be superficial. We can strike a balance between the depressors (superior part of orbicularis oculi, corrugator and procerus) and elevators (paired frontalis) and alter brow position. Medial brow elevation can be achieved by treating the glabella, and lateral brow elevation can be achieved by undertreating the lateral forehead (frontalis) and injecting the superior lateral portion of orbicularis oculi.

Bunny lines or nasal scrunch is produced by excessive activity of the nasalis muscle. Patients develop radial lines on the nasal dorsum when they smile or laugh. Vertical and radial perioral lines occur in ageing-related skin changes and habitual lip pursing (as done during smoking). There is a potential side effect of oral incompetence and treatment is therefore not recommended in wind instrument players, vocalists or scuba divers. Angle of mouth or marionette lines are the result of hyperactivity of the depressor anguli oris muscle giving the patient a sad look or a downward curl of the lips. An excessive dose or injection at a site near to the orbicularis oris can weaken this muscle, producing lip drooling and an inability to pucker the lips.

Platysmal bands are the prominent vertical bands that may develop in the neck as part of the ageing process. These vertical bands are the anterior part of platysma and injection with the toxin softens them. A prominent mentalis muscle can produce a horizontal crease or a cobblestoned appearance on the chin. Masseter hypertrophy can cause a square jaw line, widening the face and giving what is considered a more masculine appearance. Injection of the muscle with botulinum toxin can give a more oval-shaped contour to the face.

FILLERS

Different products can be inserted under the skin in different layers to improve angles, lines, folds, scars and flaccidity. The idea is to replace an original volume lost by the ageing process or to create volume. Fillers can be temporary or permanent. Permanent fillers are in our view no longer recommended, as the long-term safety of their use has not been established conclusively. The filler with long-term effect is autologous fat grafting. This technique was popularized and modified by Coleman.[26] As certain faces age, they get thinner, and Lambros[27] does fat injections in every patient undergoing rhytidectomy.

There are, however, some issues surrounding fat transfer. Injected fat can grow – the greatest long-term problem with fat. We have seen increasing numbers of people who have gained weight after their fat injections and whose faces are growing in an unaesthetic manner. Fat is difficult to remove and fat grafts are not reliable. They work better in younger people and the adipocyte survival can be unpredictable, hence they may work better on one

side of the face than the other so touch-up procedures are often necessary. If we tell patients that fat grafting will give them a young-looking face that is smooth, round, full and wrinkle-free, we may end up ballooning the face and removing all the definition and delicacy of the face in a process that is not reversible. The most common complication of fat grafting happens when it is used in the lower lids. Fat survives very efficiently in this area, lumpiness occurs often and it is very noticeable. Around the eyes, temples and nose, temporary hyaluronic acid fillers last up to 3 years, making them a cost-effective, predictable treatment, which gives a smoother result.

Temporary fillers are metabolized by the human body and consist of different substances including collagen, hyaluronic acid, alginates and other polysaccharides. Substances such as polylactic acid and hydroxylapatite have a longer half-life. The most common temporary filler used today is hyaluronic acid (HA), a natural polysaccharide and a component of human dermis and epidermis. HA fillers offer excellent biocompatibility and provide the same structural and mechanical properties of normal subcutaneous tissue. Natural hyaluronan is rapidly broken down by hyaluronidase with a half-life of about 12 hours and eliminated through the lymphatics and by the hepatic metabolism to carbon dioxide and water. As HA is a normal extracellular component of skin, it can be used without skin testing, it has a high tolerability profile and corrections of displacement can easily be done by injection of hyaluronidase. Cross-linking gives HA fillers a life span of 6–18 months.[28] Factors that impact the longevity include the concentration, percentage of cross-linkage, type of cross-linkage, water-binding capacity and injection technique. The final proportion of cross-linked HA and the degree of cross-linking impacts the physical characteristic of the product. The product with a higher concentration and highest degree of cross-linking experiences the least amount of degradation by enzymes and free radicals.[29] The cross-linking agents also have an impact on connective tissue reaction to injectable fillers. Injection technique can play a role in longevity. Injection into the deep dermis has been shown to increase *de novo* collagen synthesis; as the HA is degraded, therefore, novel collagen synthesis replaces the HA, which results in longer lasting correction.

Although there is some evidence that HA stimulates new collagen, the main effect is from its hydrophilic properties. When not bound to other molecules, it binds to water, giving it a viscous quality similar to 'jello'. This is the main drawback of HA; it can give an unnatural overinflated look. Within the extracellular matrix, HA contributes to moisture, but collagen contributes to the scaffolding and keeps skin tight. A newer generation of biodegradable fillers have emerged which possess bio-stimulatory properties. Polycaprolactone (PCL) microspheres of 25 nanometres (30%) in diameter in a carboxymethylcellulose gel carrier (70%) combine durability and immediate outcome. The collagen stimulating effect of the PCL has been confirmed in human skin biopsies from treated subjects.[30] The PCL-based safety has been demonstrated in clinical studies and recommendation on injection techniques are provided for the upper, mid and lower face, and zone by zone for each of these areas.

In addition to manufactured fillers, a relatively new biotechnology autograft, concentrated growth factor (CGF), demonstrates significant stimulation and acceleration of soft-tissue formation. The efficacy of this therapy lies in the local delivery of a wide range and high concentration of growth factors and proteins, mimicking and supporting physiological wound healing, reparative tissue process and local infiltration therapy. The CGF technique was developed to achieve the optimal phase separation and concentrate the factors for maximum recruitment and biostimulation. The CGF therapy is an advanced, powerful anti-ageing treatment for the ultimate natural approach to facial rejuvenation; it is free from toxins and animal products and simply uses the patient's own blood.

CGF treatment may be effective in all aspects of facial aesthetics such as non-surgical facial augmentation, lip enhancement, and treating smile lines, the forehead, cheeks, neck and décolletage.

CONCLUSION

The field of anti-ageing and facial rejuvenation is advancing rapidly and new information and new therapies are discovered almost daily. As new technologies evolve, our goal should be focused on the patient, honesty and achieving a balanced look, which may be part of an overall programme of health and self-improvement. More often than not this is achieved by a combination of tools and we believe the best combination varies with the patient's face and not with what we like to use. Ultimately, while we can have our favourite treatment, it is counterproductive to be doctrinaire about it.

KEY POINTS

- Retinoids are the most powerful, effective and evidence-based topical anti-ageing products available.
- With Botulinum toxin less is more. Avoid creating unnatural folds and a frozen face.
- Manufactured fillers are extremely popular and whilst Hyaluronic acid is safe, it binds up to one thousand times its weight in water, it is a good lubricant 'jello' but when injected in the dermis it can give an overinflated look. The newer generation polycaprolactone-based collagen stimulators restores volume and redefines contours in a more natural way.
- Autologous platelet-rich plasma injections promote tissue remodelling by increasing the expression of Type I collagen in human dermal fibroblasts.

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CHAPTER 90

HISTORY OF RECONSTRUCTIVE SURGERY

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The information in this chapter is based largely on the authors' personal bibliographies, supplemented by reference to standard texts and articles on the history of surgery.

INTRODUCTION

In order to fully appreciate the current state of head and neck reconstructive surgery it is useful to understand its evolution and development. The word plastic is derived from the Greek work *plastikos*, meaning 'to mould' or 'to give form'. The origins of reconstructive head and neck surgery likely predate this linguistic root, as the early papyri of Egypt and the Sanskrit texts of India describe the use of reconstructive procedures to correct facial deformities. Reconstructive surgery over the past many centuries has largely been focused on the correction of deformities of the head and neck. Until the end of the 19th century, 'plastic surgery', as Harold Gillies described it (see The Great Wars, below), was focused on the returning the patient to a normal state, while the cosmetic or aesthetic surgery that developed in the 20th century was essentially focused on surpassing the normal.[1] This chapter will review the history of reconstructive head and neck surgery with a focus on the developments in the 20th and early 21st century.

EARLY HISTORY

Egyptian physicians can be credited with describing some of the first efforts at facial reconstruction. The Edwin Smith Papyrus, the origins of which are dated at approximately 3000 BCE, contains some of the first descriptions of surgical management of mandibular and nasal fractures. Arguably the first documented efforts of reconstructive surgery of the nose and ear are found in the Sanskrit texts of ancient India, written approximately 2600 years ago. During this period of Indian history, reconstructive surgery of the nose and ear was highly valued, as invaders from surrounding territories would often stigmatize their victims by amputating the nose or ear. The early Hindu justice system also imposed harsh penalties on those found guilty of being unfaithful to a spouse by amputating either the genitalia or the nose. It is therefore logical that the nose, a structure of dignity and unique personal identity, would become a focus of reconstructive efforts in the early history of reconstructive surgery.

In his *Sushruta Samhita* (Sushruta's compendium),[1] Sushruta, regarded as the 'Father of Indian Surgery', described a variety of surgical techniques for reconstruction of head and neck defects. Considerable controversy exists over the time period of his contributions, with dates ranging from 600 BCE to CE 1000. He contributed to many fields of medicine but is said to have laid the foundations for a variety of pedicled and rotation flaps. He was the pioneer of reconstructive rhinoplasty, and described more than 15 methods of nasal reconstruction.

ROMAN AND HELLENISTIC

Whether Hellenistic or Roman physicians were exposed to the Indian techniques through Alexander the Great's expedition to India in the 4th century BCE is of debate. Certainly Roman and Hellenistic physicians described

similar techniques to those described in India. Aulus Cornelius Celsus,[2] considered to be the greatest of the Roman medical authors and surgeons, also described a variety of techniques similar to those practiced in India in his medical text of the first century, *De Medecina*.

The royal Byzantine physician, Oribasius, wrote extensively about facial and nasal reconstruction in the 4th century. His comprehensive medical encyclopaedia, entitled *Synagogue Medicae,* followed Celsus. He described in detail the use of bi-pedicle advancement flaps for skin defects of the eyebrow, ala, cheek, nasal dorsum and columella. He described the concept of undermining of advancement flaps. His technique of alar reconstruction may have been the first description of the superiorly based nasolabial flap.

THE MIDDLE AGES AND THE RENAISSANCE

The development of facial reconstruction certainly continued in the Middle Ages. However, following the fall of Rome in the 5th century and the diffusion of Barbarians and Christianity throughout the Middle Ages, a significant decline in the advancement of all surgery, in particular reconstruction, occurred. This decline was certainly aided by Pope Innocent III, who prohibited surgical procedures of all types. It is interesting to note that physicians of the time considered surgery to be a manual skill and below their intellectual and societal stature. The concept of the barber surgeon appeared and the decline of the role of surgery and surgeons began.

The period of Renaissance in the 14th century signalled a rebirth of science, medicine and the world of surgery. In the 15th century the Branca family became prominent in wound reconstruction and the reintroduction of the Indian method of nasal reconstruction.[3] The family apparently zealously protected the techniques they had developed from outside observers and the surgical techniques were passed down through family members. Branca's son, Antonius, inherited this technique and modified it through the use of a delayed skin flap from the arm. This Italian method, as it became known, was eventually transferred to other families of surgeons.

Descriptions of these various techniques may have contributed to Gasparro Tagliacozzi's interest in nasal reconstruction. Tagliacozzi – incorrectly referred to as the originator of the Italian method – made significant contributions to facial reconstructive surgery. Working in Bologna in the latter half of the 16th century, Tagliacozzi described and refined the use of distant pedicled flaps for a variety of facial reconstructions.[4]

THE 17TH AND 18TH CENTURIES

In the late 1600s reconstructive surgery entered into a period of significant decline. This was largely based on misconceptions about transferred tissues, superstition and a lack of belief or understanding of the sciences.

Reconstructive surgery began to emerge in the late 18th century. An often-cited impetus of this renewal was a letter published in *Gentleman's Magazine* in London in 1984 by a British surgeon named Lucas. In this account, Lucas described the reconstruction of the nose of a British bullock driver whose nose was mutilated by the enemy for transporting supplies for the British forces. Lucas explained how a forehead flap was performed by an Indian man of the brickmaker caste. His account was read by a British surgeon, Carpue, who reasoned that if the procedure could be done in India it could be easily done in Britain. Carpue described his experience with two British soldiers for *Restoring a lost nose* in 1816.[5]

In 1818 the German surgeon, Carl Von Graefe, published his major work, *Rhinoplastik*.[6] Von Graefe's book described a variety of reconstructive approaches, including the Indian and Italian methods, as well as his own method utilizing a free skin graft from the arm. He also described techniques for palate reconstruction and blepharoplasty. Because of the breadth of his contributions he is regarded as one of the fathers of modern plastic surgery.

Johann Dieffenbach began his practice in Berlin in 1823, with a great interest in plastic surgery and nasal reconstruction. In 1840, following the death of Von Graefe, Dieffenbach assumed the chair at the University of Berlin and published extensively on reconstructive plastic surgery and in particular nasal reconstruction and reconstructive rhinoplasty.[7] He also made significant contributions in cleft palate repair and was one of the first surgeons to advocate the use of anaesthesia. Based on all accounts, Dieffenbach was a gifted technical surgeon and a charismatic communicator. His charm and humanitarian spirit captivated the hearts of his patients, colleagues and students. He died in his clinic while preparing for an operative procedure.

Jacques Joseph, a German orthopedic trained surgeon, is widely regarded as the father of modern rhinoplasty. His book *Nasenplastik und sonstige Gesichtsplastik*, published in 1928, remains one of the most comprehensive texts written on the subject.[8] Joseph developed a number of techniques and instruments that are still in use today.

SKIN GRAFTING

As applies to many of the reconstructive techniques used in head and neck surgery, the idea and practice of skin grafting appears to have originated in India; the Hindus reported the use of free skin grafts along with the use of forehead and other facial flaps for reconstruction. The modern interest in skin grafting likely began near the end of the 18th century when Baronio reported the use of skin grafts on sheep.

The first human skin graft was probably performed by Astley Cooper in 1817.[9] In 1869, Reverdin reported on his experience with small 2–3 mm epidermic grafts for serious burns he was treating at the Necker hospital in Paris.[10]

Ollier, who studied the work of Reverdin, emphasized the importance of the dermal component and coined the

Figure 90.1 Tagliacozzi refined the use of distant pedicled flaps for facial reconstruction.

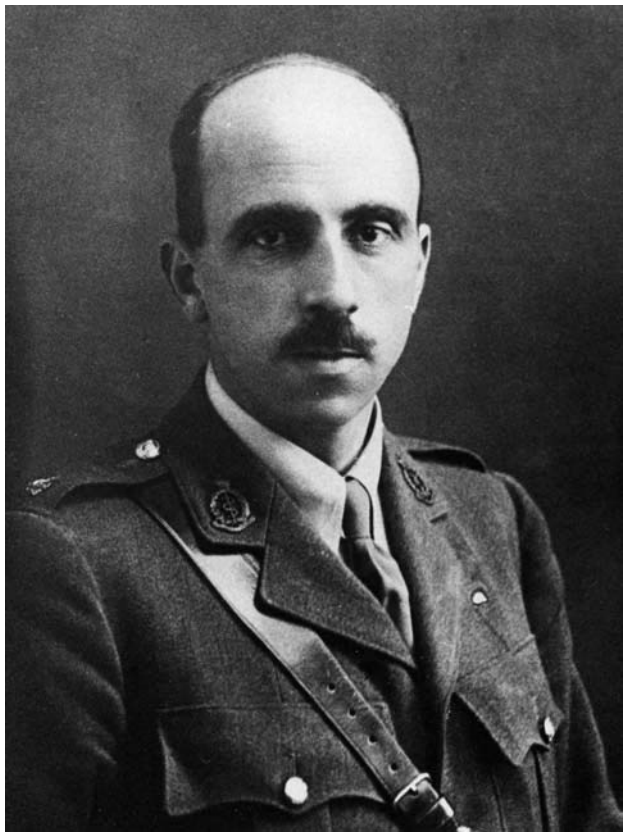

Figure 90.2 Sir Harold Gillies. Reproduced with kind permission from Andrew Bamji, Curator of Archives at the Frognal Centre, Queen Mary Hospital, Sidcup, UK.

term 'skin graft'. In 1872, Ollier performed the first successful full-thickness autograft to treat ectropion.[11]

In 1875, Wolfe described the concept of full-thickness skin grafting over a fresh surgical wound. Wolfe, an ophthalmologist by training, was given credit along with Krause for bringing this technique to clinical practice. The term 'Wolfe graft' is still used in the UK to describe a full-thickness skin graft.[12]

In 1929, Blair and Brown described the use of large split-thickness skin grafts of various thicknesses for different types of wounds characterizing the features of donor site morbidity and contraction.[13]

One of the greatest developments in reconstructive surgery was the development of the dermatome. Developed in 1939 by Padgett, a surgeon, and Hood, a mechanical engineer, it revolutionized the harvesting and application of skin grafting techniques.[14]

THE WORLD WARS

The two World Wars in the first half of the 20th century played a key role in the development of reconstructive head and neck surgery, particularly in plastic surgery, dentistry and maxillofacial surgery. The First World War presented a unique challenge for medical care because of the volume of injured combatants and the nature of the wounds (high velocity projectiles and explosions). On the first day of the Battle of the Somme the British expeditionary force suffered 60 000 casualties, 21 000 of whom were killed.

A number of surgeons had prominent roles in the primary management and reconstruction of these patients. Prominent among the French surgeons was Hippolyte Morestin. Born in Martinique, Morestin worked in the French army's surgical unit at the Val-de-Grace Military Hospital in Paris. He became well known for his expertise in local flaps, advocating the concept of wide undermining as well as developing techniques in z-plasty. Because of the nature of his work and his prominence, many surgeons went to observe his surgery.[15] Perhaps most prominent among these was Harold Gillies (1882–1960). Gillies (**Figure 90.2**) was born in Dunedin, New Zealand, and graduated in medicine from Cambridge. He trained initially in otolaryngology and in 1915 volunteered his services to the Red Cross and was sent to France. Fascinated by the reputation of Hippolyte Morestin, he went to observe his surgery. The nature of the work convinced Gillies to advocate for a specialty hospital for the treatment of facial and jaw injuries for British combatants. Interestingly, when Gillies made a return visit to observe Morestin, he was refused entry into the operating theatre.

In 1916, the British War Office established a unit at the Cambridge Military Hospital, Aldershot. The Aldershot facilities proved inadequate and in 1917 the unit was moved to The Queen's Hospital (renamed Queen Mary's Hospital in 1927) at Sidcup in Kent. Gillies treated and documented the care of numerous patients and developed his craft at Sidcup. Significant among his developments

were the refinement of the tubed flap and skin grafting for defects of the eyelid (**Figure 90.3**). Gillies' wartime experiences provided the material for his classic book, *Plastic surgery of the face*, published in 1920.16 This beautifully illustrated text set down Gillies' rules of reconstructive surgery and certainly cemented his reputation as one of the fathers of modern 20th-century plastic surgery. Gillies and Sidcup played a major role in the training of surgeons from around the world. Ferris Smith, also originally an otolaryngologist, became a prominent American plastic surgeon. Other prominent surgeons included Pickerill from New Zealand and Risdon from Canada. For his contributions to the care of the injured and his major contributions to the field, Gillies was knighted in 1930.

Between the wars, plastic and reconstructive surgery flourished in North America. In 1919, John Staige Davis published the first American plastic surgery textbook, *Plastic surgery – its principles and practice*, which became a classic in the field.[17] The 1920s and 1930s saw the development of many professional societies dedicated to plastic surgery in North America and a rapid expansion in the number of plastic surgeons in the United States.

The Second World War facilitated further developments in reconstructive surgery of the head and neck. In the UK there were only four plastic surgeons (The Big Four: Gillies, Kilner, Mowlem and McIndoe). At the beginning of the Second World War the emergency medical services in England set up nine centres for facial and jaw injuries. McIndoe was appointed to the Queen Victoria Hospital in East Grinstead, Sussex, and Gillies was sent to head the unit at Rooksdown House, Park Prewett Hospital, Basingstoke. Gillies continued to develop his expertise in facial reconstruction; McIndoe became famous for developing innovative treatment approaches for severe burns, including the face, and was well known both during and after the war for his expertise and compassionate care.

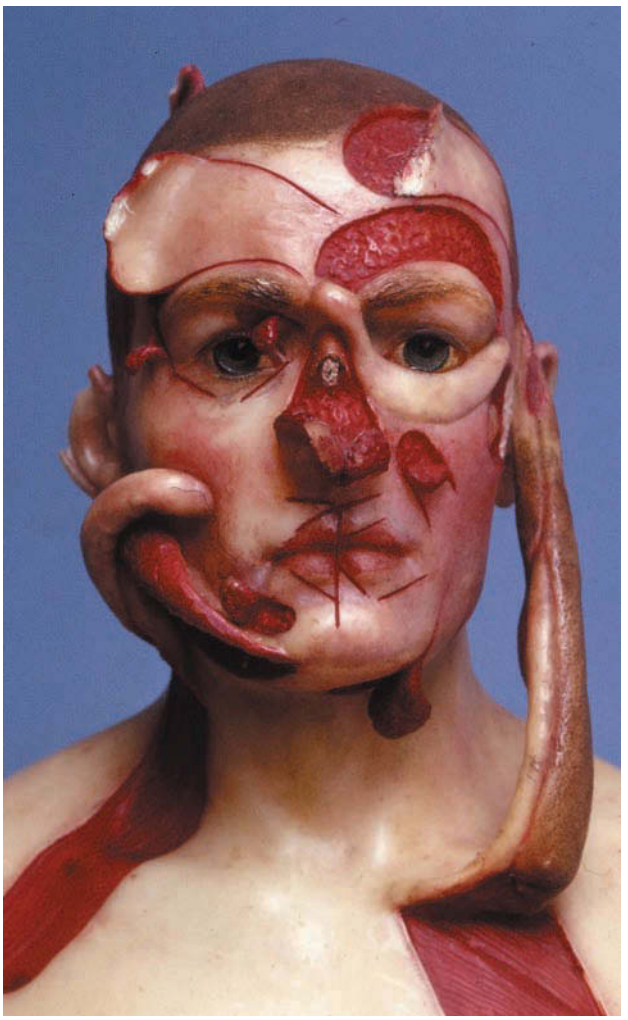

Figure 90.3 Life-size wax model of the head and upper torso, constructed for teaching purposes, illustrating surgical techniques including forehead and tubed pedicle flaps. Part of the New Zealand records returned to Sidcup in 1989 and subsequently restored at Madame Tussaud's. Reproduced with kind permission from Andrew Bamji, Curator of Archives at the Frognal Centre, Queen Mary Hospital, Sidcup, UK.

THE MODERN ERA

The expertise in soft tissue and bone reconstruction that evolved and developed during and after the World Wars changed its focus in the last 40 years of the 20th century. The emphasis on plastic and reconstructive surgery moved to the correction of congenital and secondary deformities and the reconstruction of defects following oncologic resections. Many plastic surgeons became increasingly interested in aesthetic surgery. In the 1950s and early 1960s, the majority of oncologic and post-traumatic reconstruction still utilized the techniques pioneered by Gillies and his contemporaries. In the 1960s, a number of surgical innovations changed the morbidity of head and neck reconstruction. The increasing use of axial pattern flaps made reconstruction of large oral cavity and neck defects more reliable and less costly to the patient in terms of prolonged hospitalization. Foremost among these were the descriptions of the forehead flap for oral reconstruction popularized by McGregor[18] and the deltopectoral flap described in the United States by Bakamjian.[19] In the late 1970s, the description of the pectoralis major myocutaneous flap by Ariyan[20] transformed head and neck oncologic surgery, as patients could be offered a single stage reliable reconstruction with minimal donor site morbidity. In addition, the ease of harvest and transfer of the pectoralis major flap made it a technique that any head and neck-trained surgeon could perform, broadening the scope of reconstructive surgery to other disciplines outside plastic surgery.

The late 1960s and early 1970s heralded the era of reconstructive microsurgery. The concept of free tissue transfer had been developed years earlier but was limited by the quality and availability of microvascular sutures, quality instruments and magnification. Jacobson and Suarez[21] first described the repair of vessels under 2 mm in 1960. The first free tissue transfer of a composite of skin was performed by Taylor and Daniels in 1973.[22] Subsequent developments in reconstructive microsurgery have resulted in the description of a plethora of free tissue

transfers available for head and neck reconstruction, championed by a number of extremely gifted reconstructive microsurgeons including Harii, Buncke, Manktelow and many others.

The more notable among these flaps are: the free forearm flap, described by Yang in 1983[23] and popularized for oral cavity and oromandibular reconstruction by Soutar;[24] the free fibular transfer, originally described by Taylor in 1973[22] and popularized by Hidalgo[25] for mandibular reconstruction in 1995; and the anterolateral thigh flap, described by Song[26] in 1984 and popularized for head and neck reconstruction by Wei[27] in 2002.

As experience has evolved with a vast array of free tissue transfer, creative surgeons from many disciplines and jurisdictions have developed new techniques for reconstruction of the mandible, maxilla, airway and numerous other head and neck sites. The application of these techniques has dramatically enhanced the ability of the head and neck reconstructive surgeon to deliver high quality reconstruction with preservation or restoration of form and function.

The community of specialties performing head and neck reconstruction has changed dramatically over the past 40 years. Head and neck oncologic surgery in the 1950s and 1960s was largely the domain of general and plastic surgeons, with the majority of reconstruction performed by plastic surgeons. In the last three decades of the 20th century, however, some major changes in the specialties treating defects of the head and neck evolved. Increasingly in Europe and North America, otolaryngologists with subspecialty training in head and neck surgery and reconstructive microsurgery began to develop an interest and expertise in head and neck surgery that extended beyond the treatment of laryngeal cancer. At the same time, in Europe, maxillofacial surgery began its evolution as a specialty and, increasingly, maxillofacial surgeons treated and reconstructed congenital, traumatic and oncologic defects of the head and neck.

FUTURE RESEARCH

➤ In the next 10 years, further refinements will occur in the application and evaluation of the various reconstructive microsurgical techniques. The areas of major innovation are clearly tissue engineering and transplantation. Tissue engineering may offer the potential to create composite tissue constructs that will replace the current approaches, including free tissue transfer and the associated donor site morbidity. The most notable and controversial use of tissue engineering in the head and neck site has been the airway work of Macchiarini et al.[28] Vascularized composite allografts (VCA) or transplantation clearly has the potential to dramatically change the field of reconstructive surgery of the head and neck. The recent experiences with face transplants, both in Europe and North America, have highlighted the potential of VCA as well as long-term sequelae of immunosuppression.[29, 30] As the understanding of immune surveillance and improved regimens for immunosuppression evolve, we will likely see a broader application of these techniques in head and neck reconstruction.

KEY POINTS

- Reconstructive techniques to repair facial defects and deformities have been found in ancient Egyptian and Sanskrit papyrus documents dating back over five thousand years.
- Techniques for nasal reconstruction following amputation of the nose developed in India, and were in widespread use until the middle ages.
- Pedicled flaps and free skin grafts were popularized from the late 18th-century onwards.
- Josef Dieffenbach (Berlin) is often referred to as the 'father' of plastic surgery.
- Harold Gillies pioneered techniques for facial reconstructive surgery in Britain, working mainly on servicemen with severe shrapnel injuries during the two World Wars.
- The operating microscope transformed plastic and reconstructive surgery, paving the way for free flaps.

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CHAPTER 91

GRAFTS AND LOCAL FLAPS IN HEAD AND NECK CANCER

Kenneth Kok and Nicholas White

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SEARCH STRATEGY

Data in this chapter may be updated by a PubMed search using the keywords: reconstructive ladder, skin graft, local flap, regional flap, head and neck reconstruction, wound healing, nasal reconstruction, ear reconstruction, eyelid reconstruction and lip reconstruction.

INTRODUCTION

Defects following head and neck surgery can often be closed using the technique of direct suture. This, of course, applies not only to the skin but also to the mucous membranes of the upper aerodigestive tract. This technique is used when the defect is small and where local conditions mean that enough tissue is available. However, for larger defects or in situations where direct suture is neither applicable nor available, surgical defects in the head and neck can be reconstructed with grafts, local flaps, regional flaps or free-tissue transfer. Occasionally, a combination of these different reconstructive techniques is required as 'building blocks' to reconstruct more complex defects. A **graft** is a piece of tissue that has no blood supply of its own and its survival depends on it gaining a blood supply from the recipient bed. A **flap** is a piece of tissue that has its own blood supply and does not rely on the recipient bed for its survival. This chapter focuses on the use of grafts and local flaps in head and neck reconstruction.

RECONSTRUCTIVE LADDER

The reconstructive ladder is an important concept in reconstructive surgery. It begins with the simplest option first, which is to allow the wound to heal by secondary intention. As one advances up the rungs of the ladder, more complex reconstructive techniques are encountered, up to the highest rung, which is microvascular free-tissue transfer. When analyzing a defect to be reconstructed, the reconstructive surgeon would start at the bottom rung and work his way up, deciding which reconstructive method should be undertaken. There are some instances, however, where the 'reconstructive elevator' should be taken instead and some of the rungs in the reconstructive ladder can and should be skipped. An example of this would be in the reconstruction of a significant defect in the neck following primary tumour excision with exposure of the great vessels. In this case, although a skin graft could theoretically be used and probably would 'take', the risk of exposed vessels would warrant the use of a pedicled or free flap for reconstruction. An example is shown in **Figure 91.1**.

WOUND CLOSURE AND RELAXED SKIN TENSION LINES

Many defects in the head and neck region can be directly closed if they are small and enough tissue is available locally. For larger defects, closure of the wound can be achieved by the different rungs of the reconstructive ladder, dependent on the site, size and extent of the defect. The concept of relaxed skin tension lines is useful when considering where to place skin incisions. These are lines parallel to the natural skin wrinkles and tend to be perpendicular to

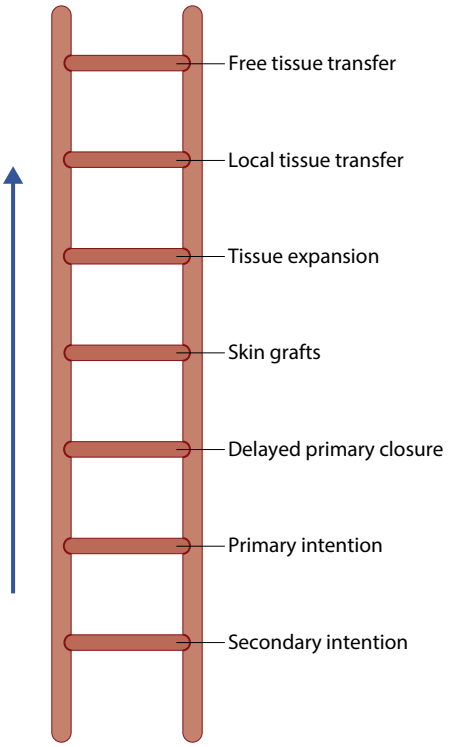


Figure 91.1 The reconstructive ladder.

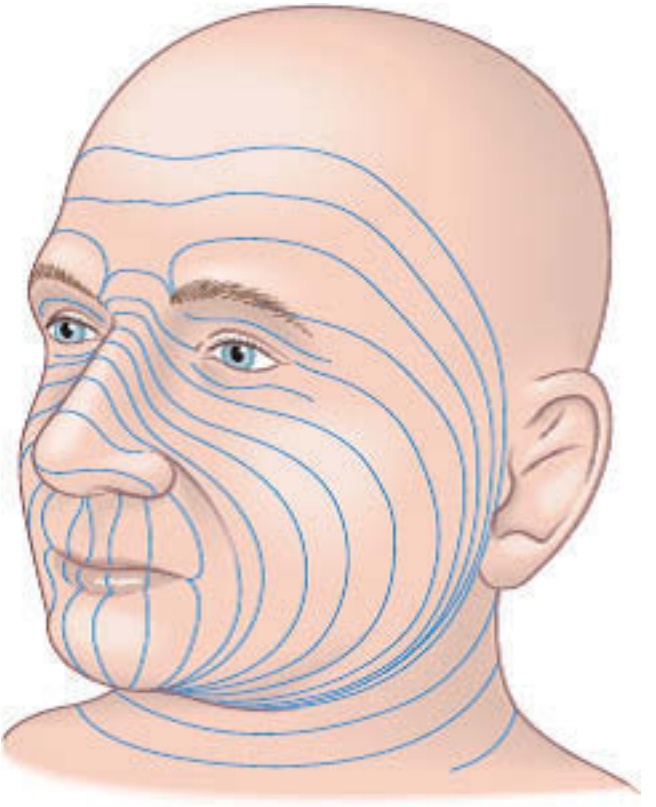


Figure 91.2 Relaxed skin tension lines.

the underlying muscle fibres (**Figure 91.2**). Scars placed parallel to these lines will be under the least amount of tension and therefore will result in the best possible scar. With regards to local flaps, these lines should be considered when closing the flap's donor site, again to minimize tension and allow easy closure.

Wedge excision

Lesions located at the free edge of tissues such as the eyelid, lips and helical rims can be excised as a wedge and repaired. The separate components of these composite tissues must be repaired individually to optimize function and appearance. These layers are, in the lip, the mucosa, orbicularis oris and skin; in the eyelid, conjunctiva, tarsal plate, orbicularis oculi and skin (**Figure 91.3**).

COSMETIC SUBUNITS OF THE HEAD AND NECK

The face is divided into multiple cosmetic subunits (**Figure 91.4**). These cosmetic subunits should be taken into account when reconstructing defects in the head and neck to optimize cosmesis. Ideally, individual subunits should be reconstructed separately and scars should not cross the subunits if possible. It is therefore preferable to use a graft or a flap to reconstruct one cosmetic subunit and a second graft or flap to reconstruct an adjacent subunit. If more than 50% of a cosmetic subunit is involved, it may be desirable to excise the entire subunit and reconstruct it to obtain an optimal result.

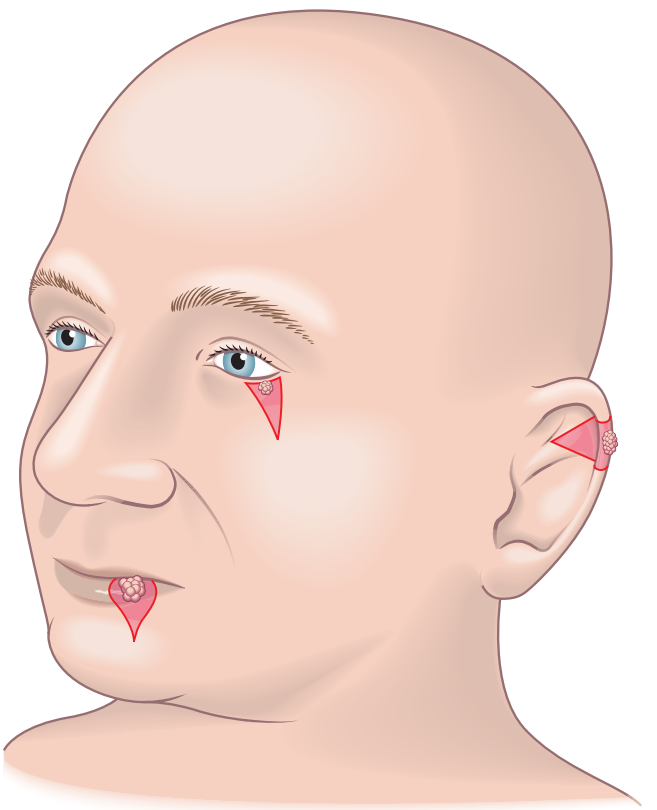


Figure 91.3 Wedge excision designs in different areas.

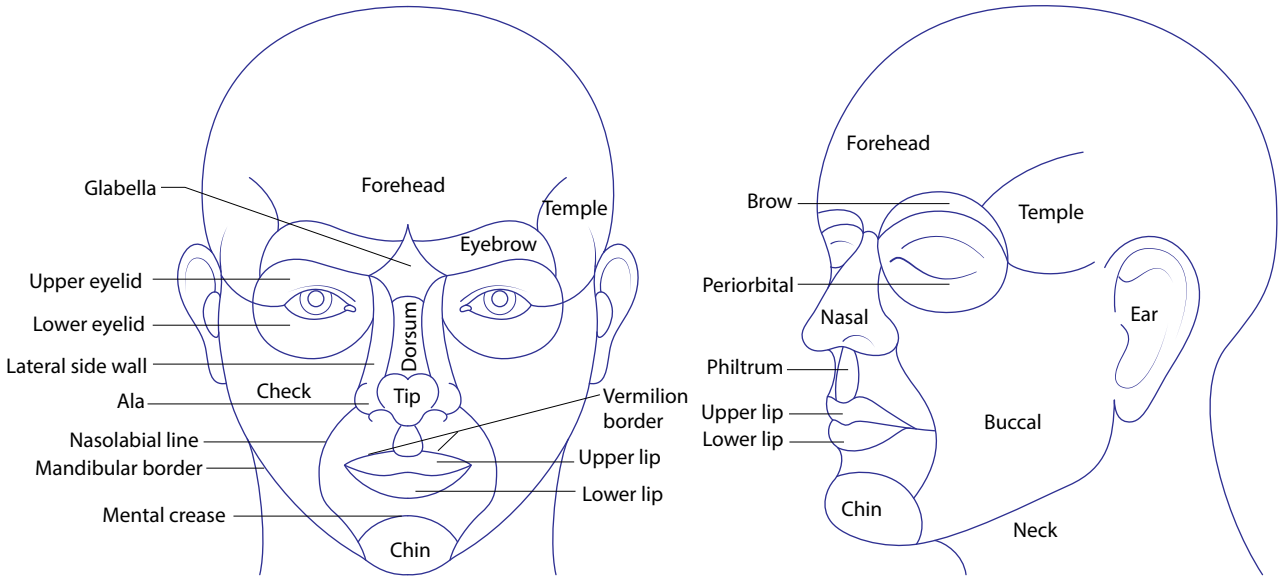


Figure 91.4 Facial cosmetic units.

SKIN GRAFTS

History

Grafting of skin originated in India over 3000 years ago when surgeons took skin grafts from the gluteal region to repair traumatic defects of the face.[1] The first report in the English language was in 1817 when Sir Astley Cooper grafted a full-thickness piece of skin from a man's amputated thumb onto the stump for coverage. Lawson[2] reported successful elective full-thickness skin grafting in 1871, which was followed by Ollier,[3] a French surgeon, describing a split-thickness skin graft in 1872. Thiersch,[4] from Germany, was the first to recognize the importance of recipient site for graft survival, and in 1875 Wolfe used a full-thickness skin graft taken from the patient's forearm to treat a traumatic ectropion of the lower lid following a gunpowder explosion. Full-thickness skin grafting of the eyelids is now a procedure with which Wolfe's name has become synonymous.[5] In 1929, Brown and Blair[6] differentiated between full-thickness and split-thickness skin grafts; they identified the advantages and disadvantages of each and, using their techniques, consistent, acceptable results were achieved. Medawar[7] studied the underlying biology of healing skin grafts in the 1940s. His work described the cellular changes in both the epidermis and dermis, giving the technique of skin grafting a scientific basis and laying the foundation of modern transplant immunology.[8]

Introduction

A **graft** is a piece of tissue that is transferred from one site to another, devascularizing it in the process. The area from which the graft is taken is known as the **donor site** and the area to which the graft is applied is known as the **recipient site**. Grafts can be classified according to their composition – skin, bone, cartilage, fat, mucosa, or composite grafts which consist of two or more different tissue types[9] (e.g. a septal mucosal graft consisting of septum and mucosa). They can also be classified according to their source. An **autograft** is a graft taken from one part of an individual's body and transferred to a different part of that same individual. An **isograft** is a graft transferred between genetically identical individuals, such as between identical twins. An **allograft** is transferred from one individual to another of the same species. A **xenograft** is a graft transferred between different species.

Skin grafts are of two types: **split-thickness** skin grafts (STSGs) or **full-thickness** skin grafts (FTSGs) dependent on the dermal content of the graft. FTSGs contain epidermis and all of the dermis whereas STSGs contain epidermis and a variable amount of dermis (thin, intermediate or thick) (**Figure 91.5**).

Skin graft healing

Once a skin graft has been harvested, it has been detached from its blood supply and is, temporarily, not viable. In order to survive permanently, it has to become reattached and obtain a new blood supply from its recipient site; this process is known as 'take'. Skin graft take is a continual biological process but, for convenience, it can be divided into four main stages (**Table 91.1**):

1. Skin graft adherence (immediate)
2. Serum imbibition (first 24–48 hours)
3. Revascularization (48 hours to 3 weeks)
4. Remodelling (3 weeks to 1 year)

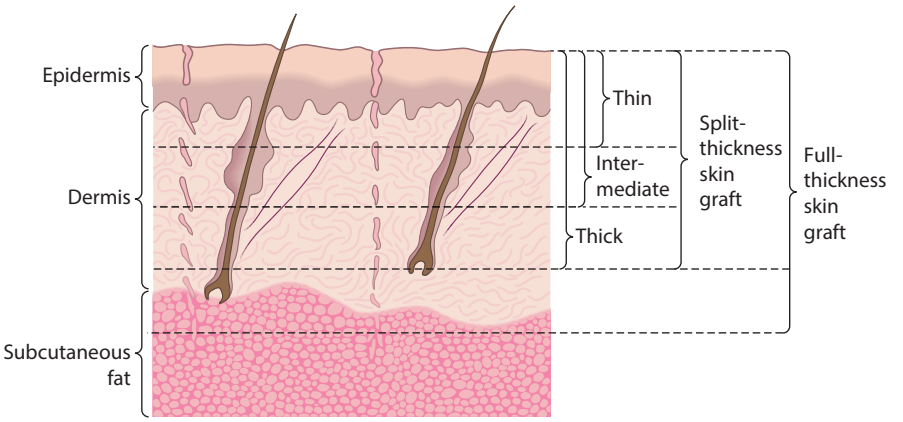


Figure 91.5 Skin graft thickness.

TABLE 91.1 Graft healing

Stages of graft healing	Time period	Mechanism
Graft adherence	Immediate	Graft adheres to recipient bed through formation of fibrin layer
Serum imbibition	Up to 48 hours	Graft survives via absorption of nutrients from a recipient bed
Revascularization	48 hours to 3 weeks	Inosculation – joining up of cut vessel ends in graft and recipient bed Revascularization – ingrowth of vessels into the graft producing new vascular channels Neovascularization – ingrowth of vessels down basement membrane
Remodelling	3 weeks to 1 year	Maturation and remodelling of the graft with collagen reorganization

Initially, when the graft is applied, it becomes adhered to the recipient bed by the formation of an intervening layer of fibrin.[10] Within 48 hours, the thin fibrin layer starts to break down and adhesion to the bed is maintained by the proliferation of fibroblasts and the deposition of collagen.[11] During this period of initial adherence, the skin graft survives through the passage of nutrients from plasma leaking from capillaries in the recipient bed. This is known as serum imbibition.[12] During this time, the graft gains weight and swells. The skin graft, however, cannot depend on serum imbibition indefinitely and, after 48 hours, revascularization of the graft begins to take place. There are several methods by which this occurs: namely inosculation, revascularization and neovascularization.

- **Inosculation** is the process of the joining up of the cut ends of the vessels in the recipient bed with the cut ends of vessels in the skin graft.[13]
- **Revascularization** is the actual ingrowth of vessels into the graft to produce new vascular channels.
- Alternatively, the endothelium of old cut vessels degenerate, leaving behind its basement membrane and this acts as a conduit for growth of capillary buds. This is known as **neovascularization**.[14]

All these processes continue for up to 3 weeks until revascularization of the graft is complete. Once the graft has become revascularized, it undergoes maturation and remodelling with collagen reorganization and increasing strength.

Factors affecting graft healing

Successful take of a skin graft is dependent upon the extent and speed at which vascular perfusion is returned to the graft. This is determined by graft factors, local and systemic factors. To obtain successful graft take, each of these factors must be optimized.

FTSGs have a higher metabolic demand due to their thickness and therefore have a higher chance of failure compared to STSGs. Local factors, such as the vascularity of the wound bed, are also an important determinant in graft take. Healthy granulation tissue, muscle and fascia act readily as recipient beds whereas fat is less suitable. Bone covered with periosteum will accept a graft but exposed bone and tendon will not. In some cases, exposed bone (such as the outer table of the skull) can be burred to cause pinpoint bony bleeding which will facilitate graft take.

In order for vascular channels to form between the recipient bed and graft, the graft has to be immobilized and in direct contact with the recipient bed. Shearing forces must be avoided and numerous methods such as tie-over dressings, the use of foam and sponges, and bandaging have been described to facilitate graft take. The most frequent cause of graft loss is the presence of a haematoma or a seroma which separates the graft from its recipient bed. Meticulous haemostasis and either meshing or fenestrating the graft to allow fluid to escape will help to prevent this. Infection is another common cause of graft loss and wounds that contain more than 10^5 organisms will not support a graft. Grafted beds which

become infected should be treated with systemic and/or topical antibiotic agents to reduce the risk of graft loss. Common pathogens include *Streptococcus pyogenes*, *Pseudomonas aeruginosa* and methicillin-resistant *Staphylococcus aureus*, which can all destroy fibrin and prevent graft adherence.[15]

In addition to these local conditions, systemic conditions of the patient can also influence skin graft take. These include diabetes mellitus, smoking, previous radiotherapy and chemotherapy, as well as nutritional status.

Split-thickness skin graft vs full-thickness skin graft

The amount of dermis included with the graft determines both the likelihood of survival and the degree of contraction. All skin grafts contract once removed from their donor site (primary contraction) and again following revascularization (secondary contraction). Primary contraction occurs as a result of the elastin within the dermis whereas secondary contraction occurs due to myofibroblast activity within the wound bed. STSGs can tolerate less vascularity than FTSGs, and undergo less primary contraction but more secondary contraction. They also tend to have abnormal pigmentation, are more susceptible to trauma and usually have poorer sensory recovery. STSGs are hairless due to the lack of hair follicles (see **Figure 91.5**).

FTSGs require a better vascular bed for survival than STSGs and they undergo more primary contraction but less secondary contraction. FTSGs also resists trauma better, tend to provide a better colour match and have improved sensory recovery due the greater availability of neurilemmal sheaths within the dermis. FTSGs also contain hair follicles and will demonstrate similar hair growth to the donor site. These differences are summarized in **Table 91.2**.

Composite grafts

Composite grafts are grafts which contain two or more different tissue types. An example that was used previously is a septal mucosal graft which contains septum and mucosa. Another example is a chondromucosal graft from the ear which contains cartilage and skin. These grafts are useful in reconstructing composite defects, either for complete reconstruction, as in the reconstruction of an alar rim or small defect of an ear, or as partial reconstruction of a more complex composite defect. An example of one such defect is the eyelid where three separate layers (i.e. the mucosa, tarsal plate and skin) need to be reconstructed. In this case, a septal mucosal graft can be used to reconstruct the mucosa and tarsal plate support and a cheek rotation flap can be used to reconstruct the skin defect (**Figure 91.6**).

TABLE 91.2 Advantages and disadvantages of STSGs vs FTSGs

Factor	STSG	FTSG
Amount of dermis	Variable	All of dermis
Chance of successful take	More likely	Less likely
Graft contraction	More contraction	Less contraction
Colour match	Abnormal pigmentation	Better colour match
Robustness	Less robust	More robust
Sensory recovery	Limited	Better
Donor site healing	Heals secondarily	Heals through primary intention
Size of graft	Large grafts can be harvested	Limited due to need for primary closure of donor

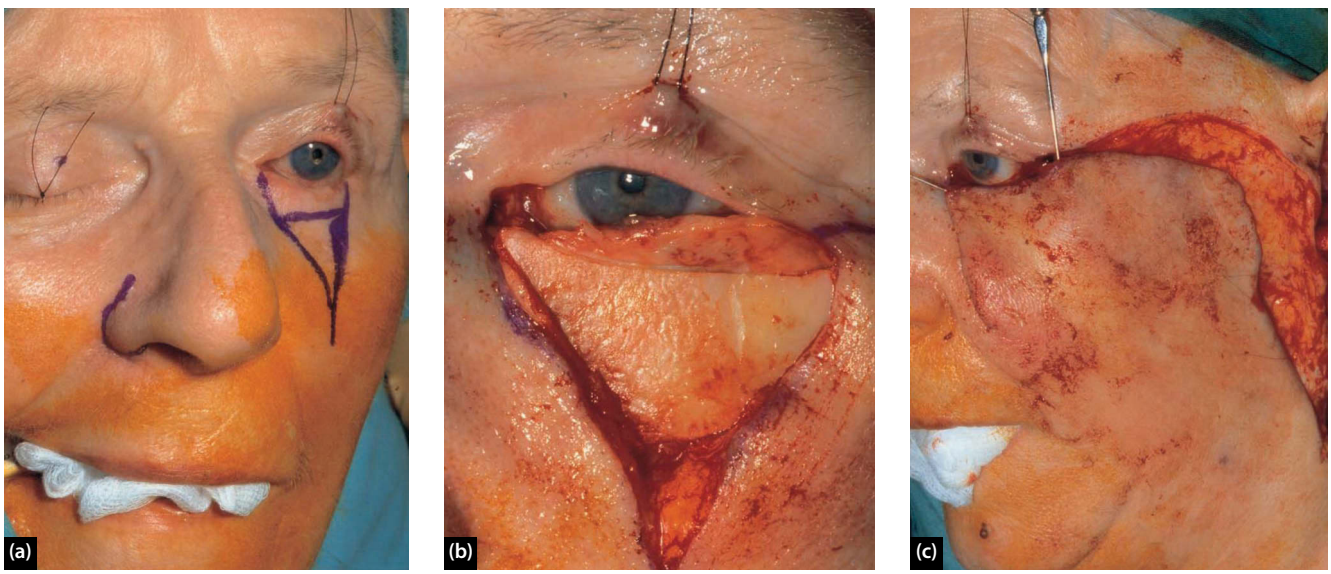


Figure 91.6 (a) Wedge excision marked with access incision in right alar crease for septal cartilage graft harvest. **(b)** Septal cartilage graft *in situ*. **(c)** Cheek rotation flap raised and inset to defect.

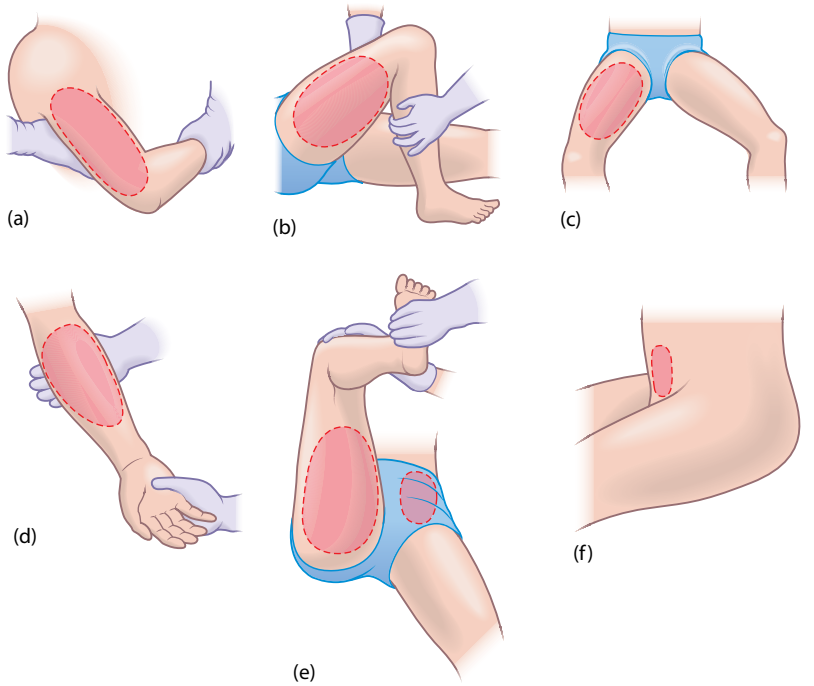


Figure 91.7 Split-thickness skin graft donor sites.

Skin graft donor sites

After an STSG is harvested, the donor site heals by re-epithelialization from adenexal structures, such as hair follicles and sweat glands, in the remaining dermis. Resurfacing occurs by the migration of keratinocytes from these structures to cover the wound. As there is no remaining epithelium in FTSG donor sites, the wound needs to be closed directly. This limits the amount of skin that can be harvested and the size of the defect that can be reconstructed using a FTSG. STSGs can be taken from anywhere on the body.[16] Commonly used areas include the thigh, trunk and buttocks as shown in **Figure 91.7**.

The graft is harvested with either an air- or battery-powered dermatome or a hand knife such as a Watson knife. The standard thickness which is preset on a dermatome is 0.3–0.4 mm or 10–12/1000 of an inch. The skin can then be either meshed or fenestrated by hand. The donor site is dressed with a non-adherent dressing[19] and left undisturbed for approximately 14 days. Most STSG donor sites are healed by 21 days with minimal scarring but they may be discoloured and susceptible to sunburn for up to 2 years afterwards.

The thickness and colour of skin varies greatly from different parts of the body and this affects the choice of FTSG donor site. Commonly used sites are pre- and post-auricular, the supraclavicular fossa, the antecubital fossa and the groin, as shown in **Figure 91.8**.

The FTSG is harvested with a scalpel and is closed directly with sutures to leave a linear scar. The amount of skin that can be taken is limited by the need to obtain a tension-free closure of the donor site. Examples of the use of a skin graft in the head are shown in **Figure 91.9**.

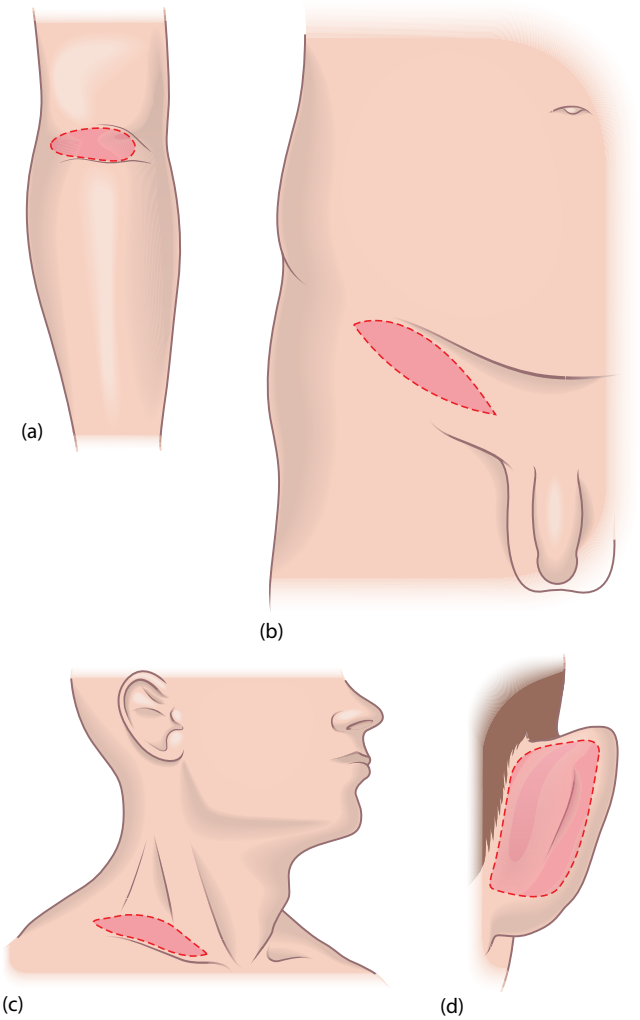


Figure 91.8 Full-thickness graft donor sites.

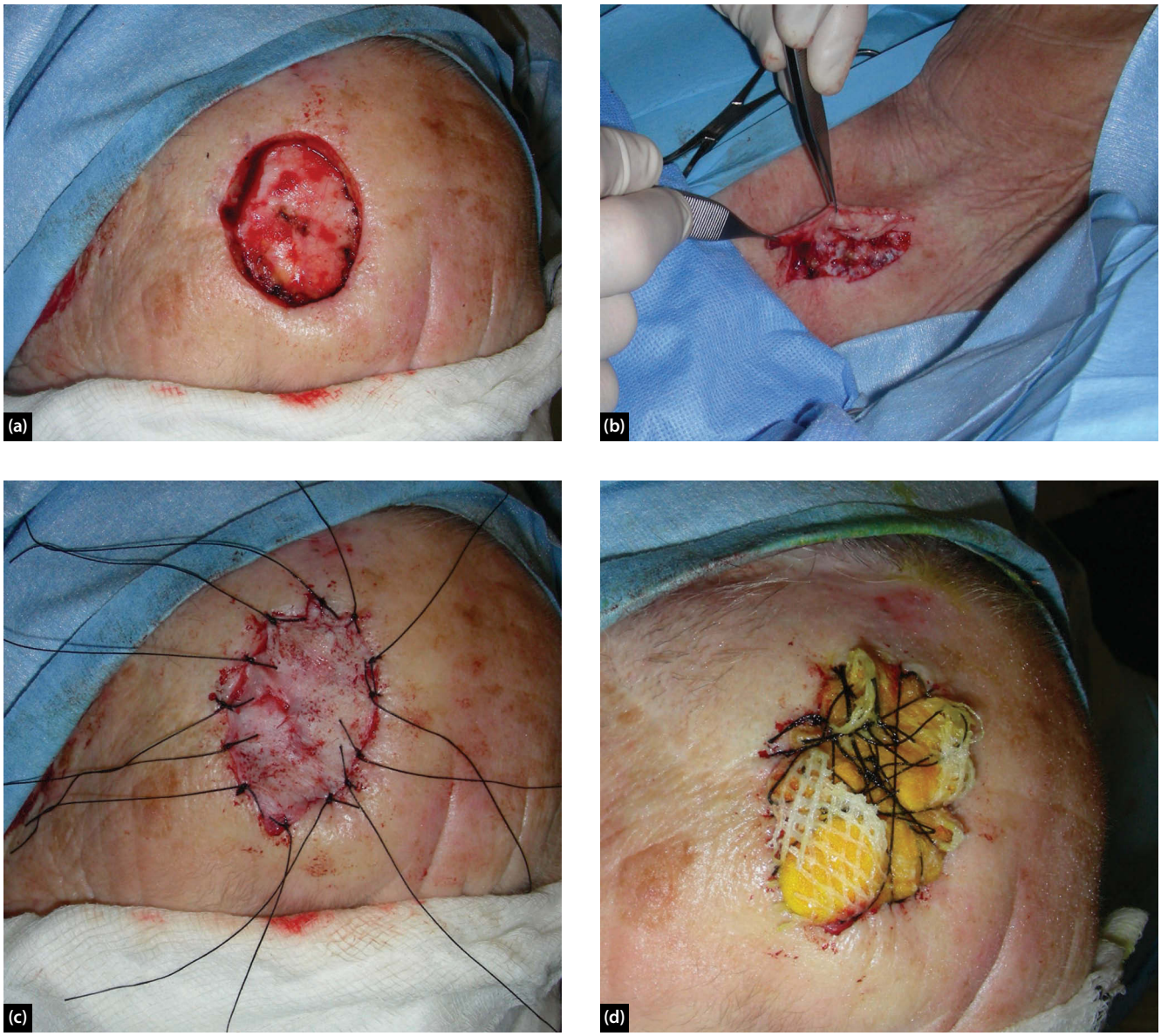


Figure 91.9 (a) Scalp wound following skin cancer excision. **(b)** Full-thickness graft harvest. **(c)** Full-thickness graft secured. **(d)** Gelonet and proflavin wool tie-over dressing.

LOCAL FLAPS

Basic principles

A flap, unlike a skin graft, has its own blood supply. Flaps are useful in reconstructing defects with poor vascularity, exposed vital structures and where skin grafts are inappropriate or would lead to poor cosmesis. Flaps are also useful in reconstructing defects where post-operative radiotherapy is planned as they are less susceptible than skin grafts to the ill effects of radiotherapy.

Flaps can be classified according to their circulation, composition, contiguity or contour. The circulation of flaps may be random, which means that the blood supply is from a non-named vessel in the base of the flap, or axial, which means that they are based on an anatomically recognized artery.[17] Flaps can be composed of different tissue types, such as skin, fascia and skin (fasciocutaneous), muscle or muscle and the overlying skin paddle (myocutaneous). The contiguity of a flap relates to the distance between its source and the defect to be reconstructed. This can be local, regional, distant or free. A local flap is composed of tissue adjacent to the defect. A regional flap is from the same anatomical region as the defect (e.g. forehead flap for nasal reconstruction). A distant flap is from a different part of the body away from the region of the defect (e.g. pectoralis major flap in head and neck reconstruction). A free flap is completely detached from the body and anastomosed to recipient vessels close to the defect. The contour of the flap relates to the method in which it is transferred into the defect. It can either be advanced or moved about a pivot point.

A flap is inset into a primary defect. The secondary defect is the site from which the flap is raised. This is

usually closed directly but can be grafted or closed by another flap. When designing a local flap in the head and neck, the two most important considerations are appreciation of the relaxed skin tension lines (see **Figure 91.2**) and the cosmetic units (see **Figure 91.4**). It is preferable to reconstruct an entire cosmetic unit with a single flap to optimize cosmesis and, in some cases, it may be necessary to excise the remaining tissue beyond the boundary of the original defect to facilitate this. This is particularly important if more than 50% of the cosmetic unit is involved. If the defect involves two cosmetic units, then two flaps (one for each unit) may be preferred. The donor area from the flap should be from the same cosmetic unit or one adjacent if possible and should not transgress multiple units. Ideally, the scar from a direct closure of a secondary defect should be in a relaxed skin tension line as it will be under the most tension of any part of the flap.

Flap planning is crucial to the success of the reconstructive procedure. When planning a random flap, the breadth of the base should be no more than the length of the flap to prevent necrosis of the flap (a ratio of 1 : 1). In the head and neck region, the blood supply is good so this can be extended to a ratio of base breadth to flap length of 1 : 1.5. For axial flaps, the length to breadth ratio is much greater but it is important to delineate and protect the named blood supply to the flap. Reverse planning is an important principle in flap design. This is a technique where a template of the primary defect is reflected from the defect to be reconstructed onto the flap donor area from a fixed point, usually the pivot point of the flap, to help assess where the flap needs to be raised from to provide sufficient defect coverage as well as minimal donor site morbidity.

Advancement flaps

Advancement flaps are moved forward into a defect without any rotation or lateral movement. They may be simple or modified. A simple advancement flap relies on the skin's elasticity to cover the primary defect. There are a number of ways in which advancement flaps can be modified to aid advancement. Burow's triangles are triangles of skin that are excised at either side of the base of the flap to equalize the length between the sides of the flap and the adjacent wound margin. These help in allowing the flap to advance, as demonstrated by a Rintala flap[18] being used to cover a defect of the nasal tip (**Figure 91.10**). A V–Y flap is another modified advancement flap. The flap itself is raised as a triangular (or 'V'-shaped) flap. When is it advanced, the secondary defect is closed directly, leaving a 'Y'-shaped scar. An example of one such flap is the nasolabial V–Y advancement flap shown, which is an axial flap based on either the superior labial artery or the angular artery (**Figures 91.11**).

Bipedicled flaps

A bipedicled flap receives a blood supply from both ends as it has two bases. It is less prone to necrosis than flaps of similar dimensions which are attached at only one end. An example of this is the Tripier flap[19] for lower eyelid reconstruction (**Figure 91.12**). Skin from the upper lid based on both a medial and a lateral attachment is swung down, like a bucket handle, to provide cover for a defect in the lower lid. To increase the viability of this flap, a strip of the orbicularis oculi muscle can be included, making it a musculocutaneous flap.

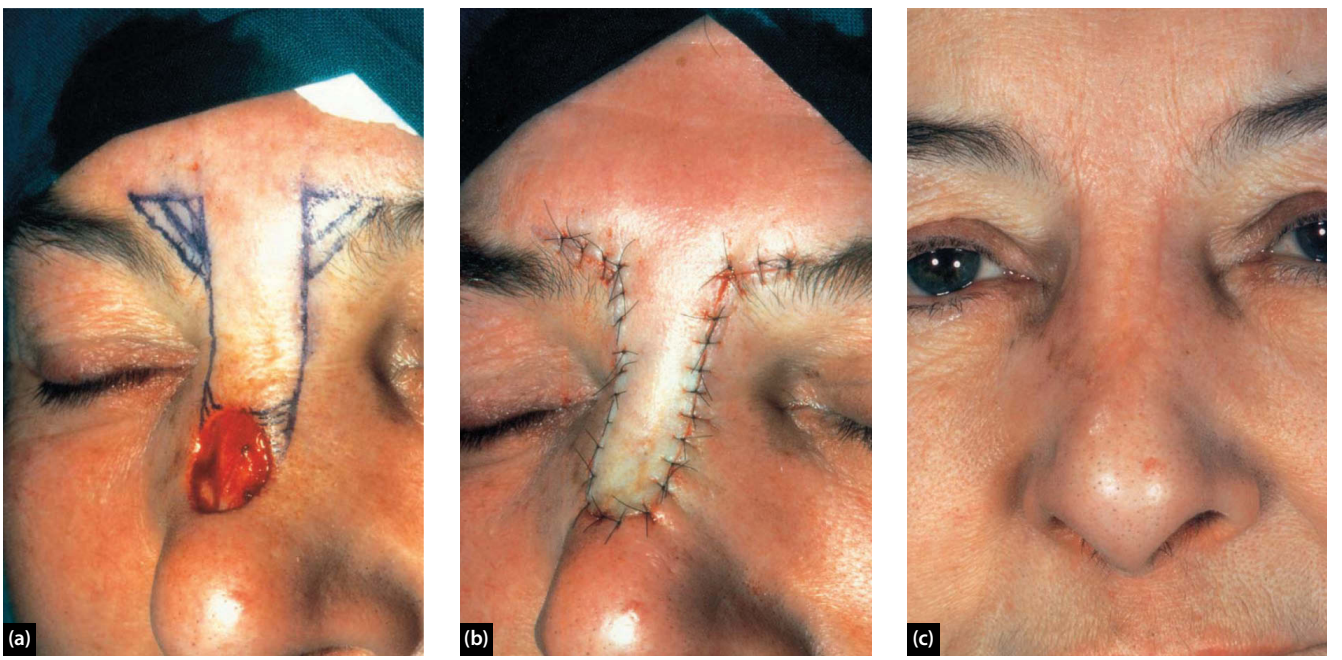


Figure 91.10 (a) Rintala flap design for dorsum of nose reconstruction. **(b)** Rintala flap raised and inset to defect. **(c)** Six-month post-operative appearance.

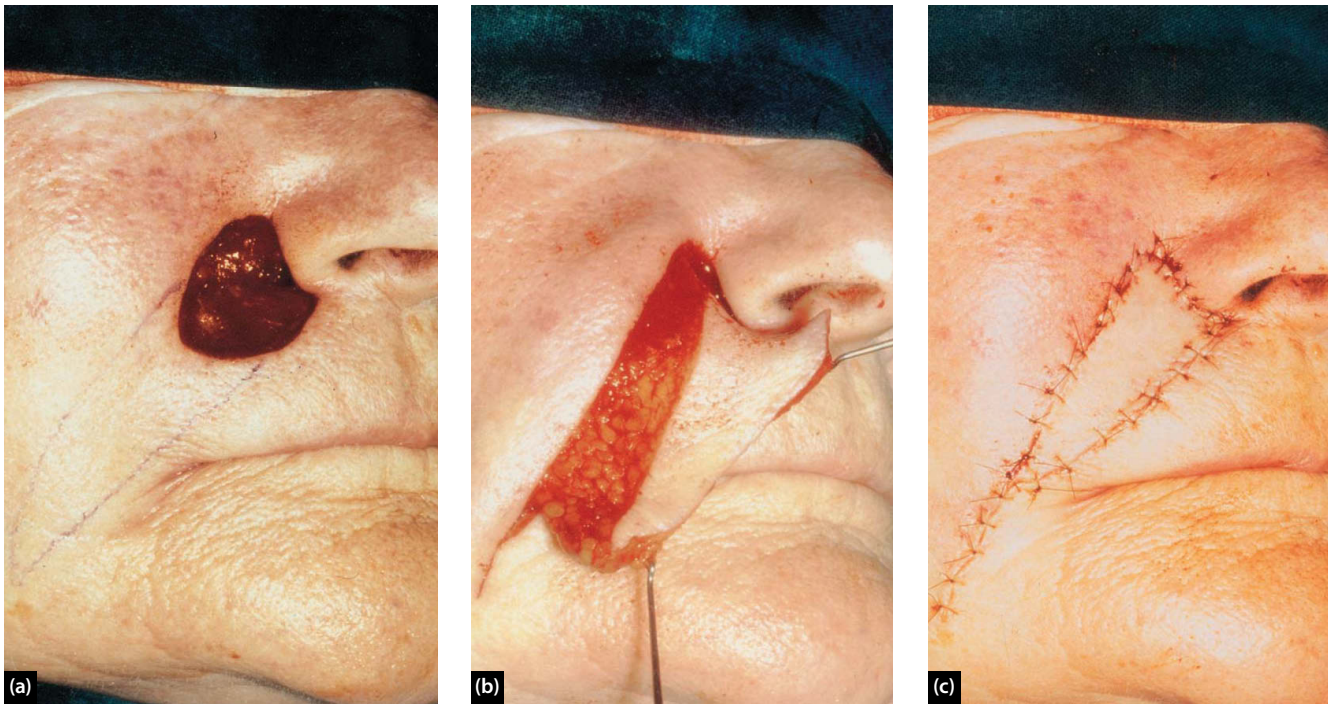


Figure 91.11 (a) Defect in right alar/nasolabial region with design of nasolabial V–Y advancement flap. **(b)** Flap raised. **(c)** Flap inset.

Pivot flaps

All pivot flaps move about a fixed pivot point and an arc which is the line of greatest tension of the flap. A pivot flap can be either a transposition flap, where the flap is moved into an adjacent defect by pivoting around the pivot point, or a rotation flap, where the flap is rotated around the pivot point into the defect (**Figure 91.13**). When a flap is transposed to cover the primary defect, the secondary donor defect is usually closed directly if possible, skin grafted, or reconstructed with a second flap. An example of this is the bilobed flap, where a second flap is raised to close the donor defect (**Figure 91.14**).

TRANSPOSITION FLAPS

A transposition flap is a flap that is moved into an adjacent defect by pivoting around its fixed point. Various types of transposition flaps have been described including the rhomboid flap, the flag or banner flap, and the bilobed flap.

Rhomboid flaps

A rhomboid flap is a type of transposition flap where the donor defect is closed directly.[20] The defect is firstly designed as a rhomboid. Each of the limbs of the defect and the flap being raised need to be of equal length and the angles of the rhomboid need to be 120 degrees and 60 degrees, respectively. The flap needs to be designed so that the donor site scar lies parallel to the relaxed skin tension lines (**Figure 91.15**). A variation of the rhomboid flap is the Dufourmentel flap,[21] which has limbs of equal lengths but angles of 150 degrees and 30 degrees. Other variations of the geometry of the rhomboid flap have been described.[22] One of these is the 'square peg in the round hole' where the primary defect is circular (as is the case in most clinical situations) and the rhomboid flap is stretched to fill the defect.[23] This reduces the need to excise the extra skin required in the standard rhomboid flap, which is particularly important in cosmetically sensitive areas such as the face.

Flag or banner flaps

A number of small transposition flaps can be used around the face and generally the donor site is closed directly. These are termed flag flaps as the piece of tissue moved resembles a flag or banner. These are normally random pattern flaps but can be based on a known artery in some parts of the head or neck. A glabellar flap is an axial transposition flag flap based on the supratrochlear artery. This allows the flap length to be three times the base breadth (**Figure 91.16**). It is transposed to cover the primary defect and the donor site is closed directly.

Bilobed flaps

A bilobed flap consists of two transposition flaps.[24] The first flap is transposed into the primary defect, the second flap is transposed into the secondary defect (the original site of the first flap) and the tertiary defect (the original site of the second flap) is closed directly. The flap should be designed so that the directly closed tertiary defect is parallel to the relaxed skin tension lines (see **Figures 91.14** and **91.15**). Theoretically, the bilobed flap uses less tissue than any other method of wound closure and because of this minimizes tension at the primary defect.[25]

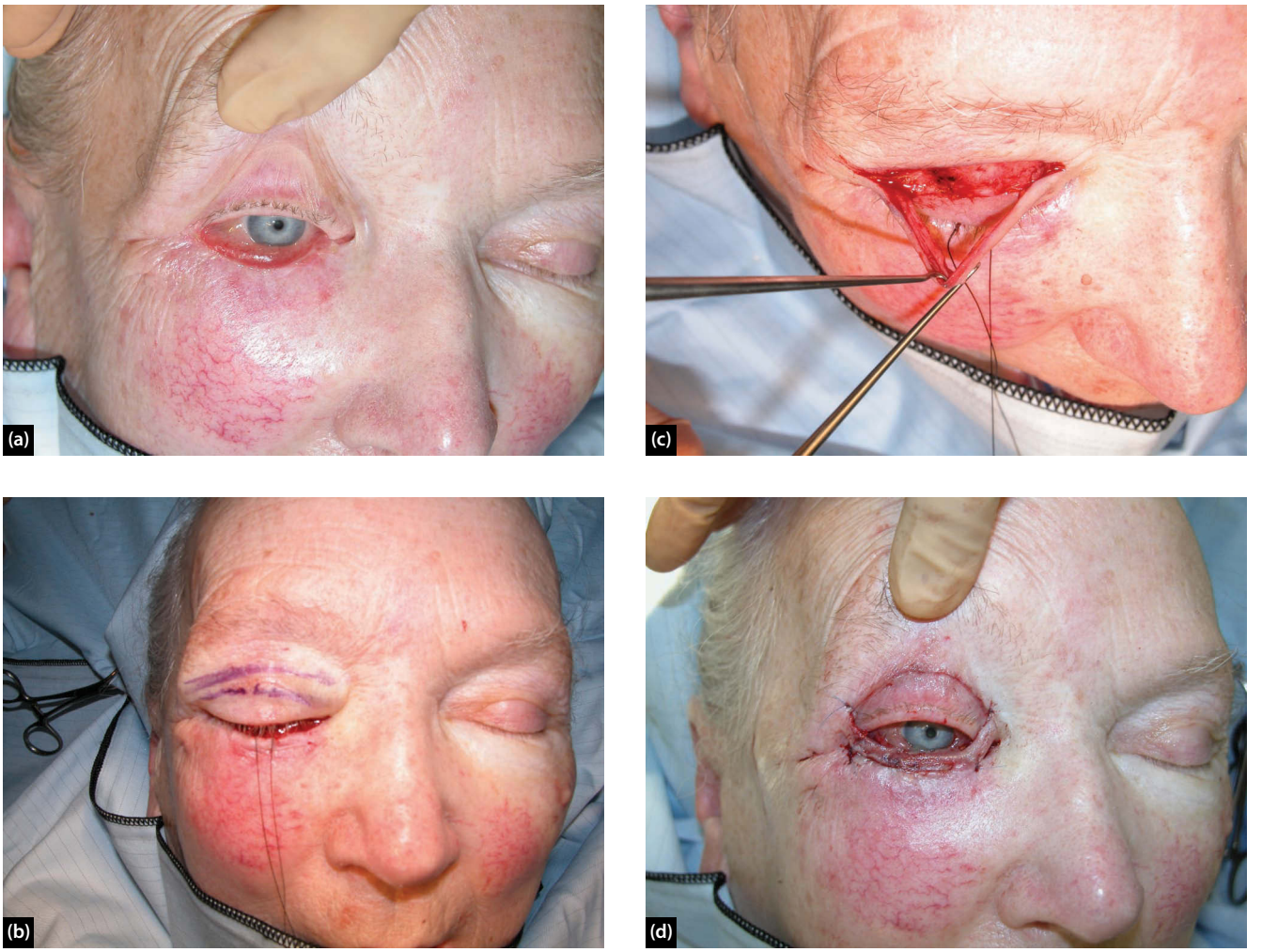


Figure 91.12 **(a)** Total lower eyelid defect. **(b)** Tripier flap design from upper eyelid. **(c)** Flap raised. **(d)** Tripier flap inset to lower eyelid defect.

The ideal use of a bilobed flap is where there is tissue available locally and where it is important to avoid producing tissue stretch. The bilobed flap is most commonly used to deal with defects at the tip of the nose. Although there is some spare tissue around this area, the nasal tip can become displaced if skin is imported to cover defects here as a local flap.[26]

ROTATION FLAPS

Rotation flaps are large flaps that rotate into the primary defect. The volume of tissue raised in the flap is high when compared to the defect being closed. Normally, the flap is a semicircle and the primary defect is 'triangulated' or designed as a triangle, adjacent to the flap. Geometrically, the flap circumference should be at least eight times the width of the defect to allow closure of the donor site; however, in practice, it is best to design the flap as large as possible as the direct closure of the donor site relies on tissue redistribution and tissue elasticity. Occasionally, the use of a Burow triangle or a back cut may be needed. A back cut releases a rotation flap that is too tight by decreasing the tension at the base of the flap, thus moving its pivot point towards the defect. This decreases the tension of closure at the site of the primary defect. A back cut that is taken too far, however, may significantly decrease the width of the flap, which will increase the chance of devascularizing it. These flaps are useful for dealing with defects of the scalp or cheek (see **Figure 91.13**).

RECONSTRUCTION OF SPECIFIC ANATOMICAL REGIONS OF THE HEAD AND NECK

Scalp

ANATOMY

The scalp has five distinct anatomical layers. From superficial to deep, these are the skin, subcutaneous connective tissue, muscle or aponeurosis (galea), loose areolar tissue and pericranium. The skin of the scalp is the thickest on

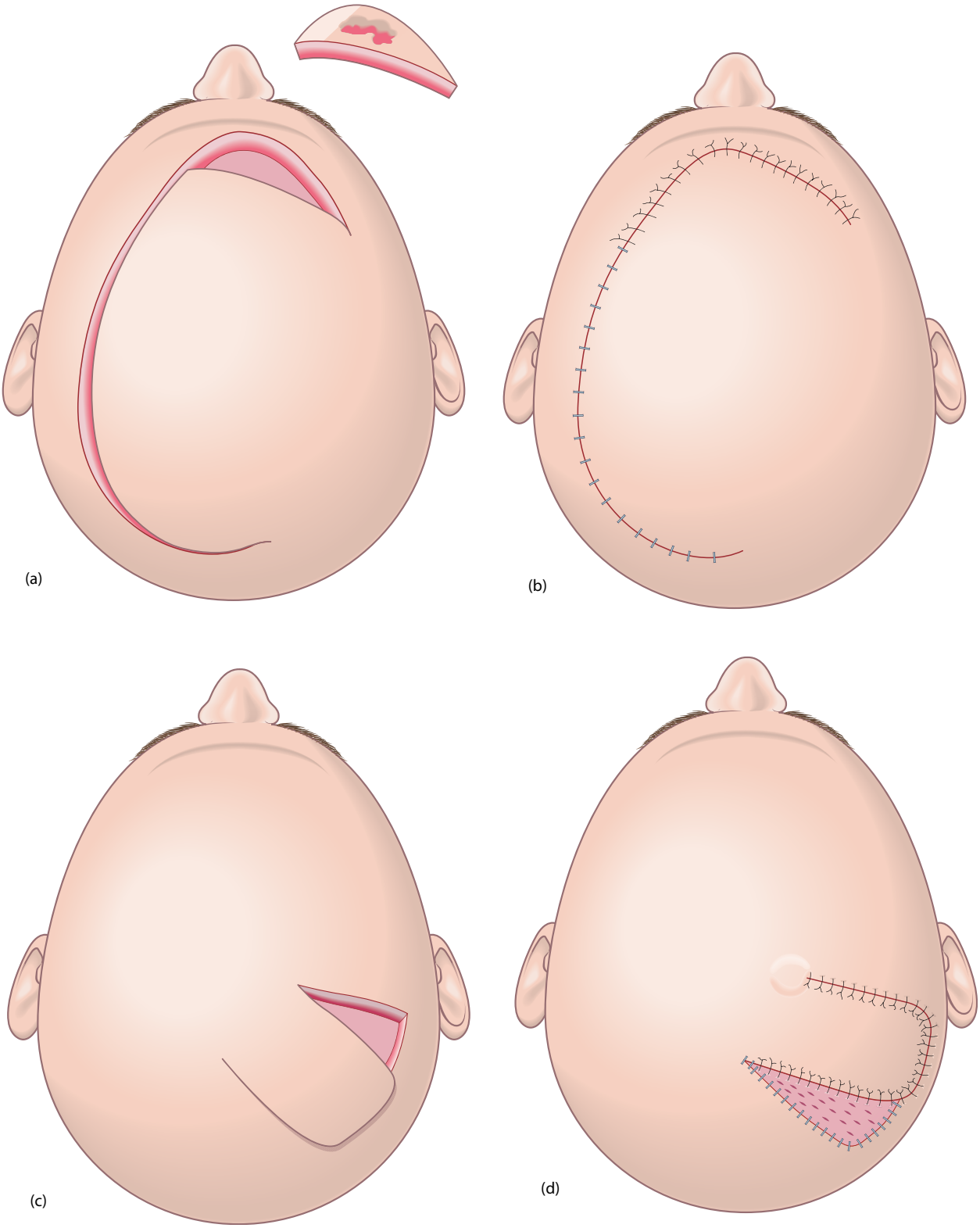


Figure 91.13 Scalp transposition and rotation flap design.

the human body, ranging from 3 mm to 8 mm. Beneath the skin, the subcutaneous tissue contains the vessels and nerves supplying the scalp. Deep to this is the musculoaponeurotic layer consisting of the frontalis muscle anteriorly and the occipitalis muscle posteriorly. These muscles are connected by an aponeurotic layer (the galea aponeurotica). Laterally, this aponeurosis is connected to the subcutaneous musculoaponeurotic system (SMAS) of the face.

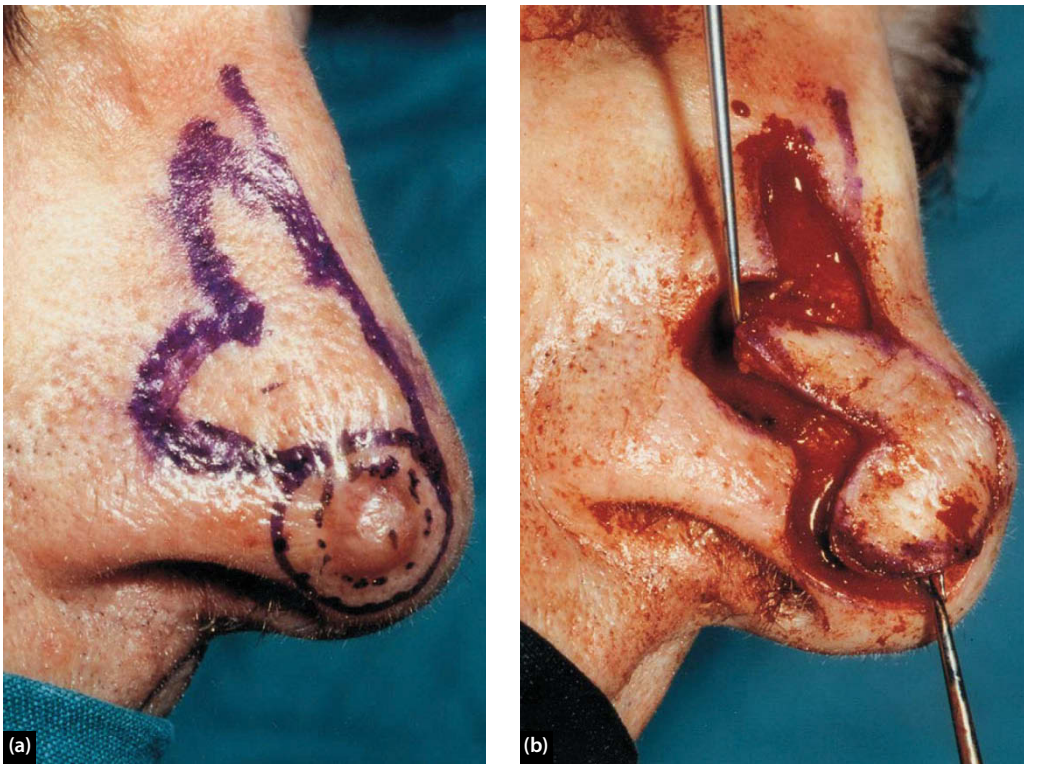


Figure 91.14 (a) Basal cell carcinoma excision marked with bilobed flap design. **(b)** Bilobed flap raised and inset.

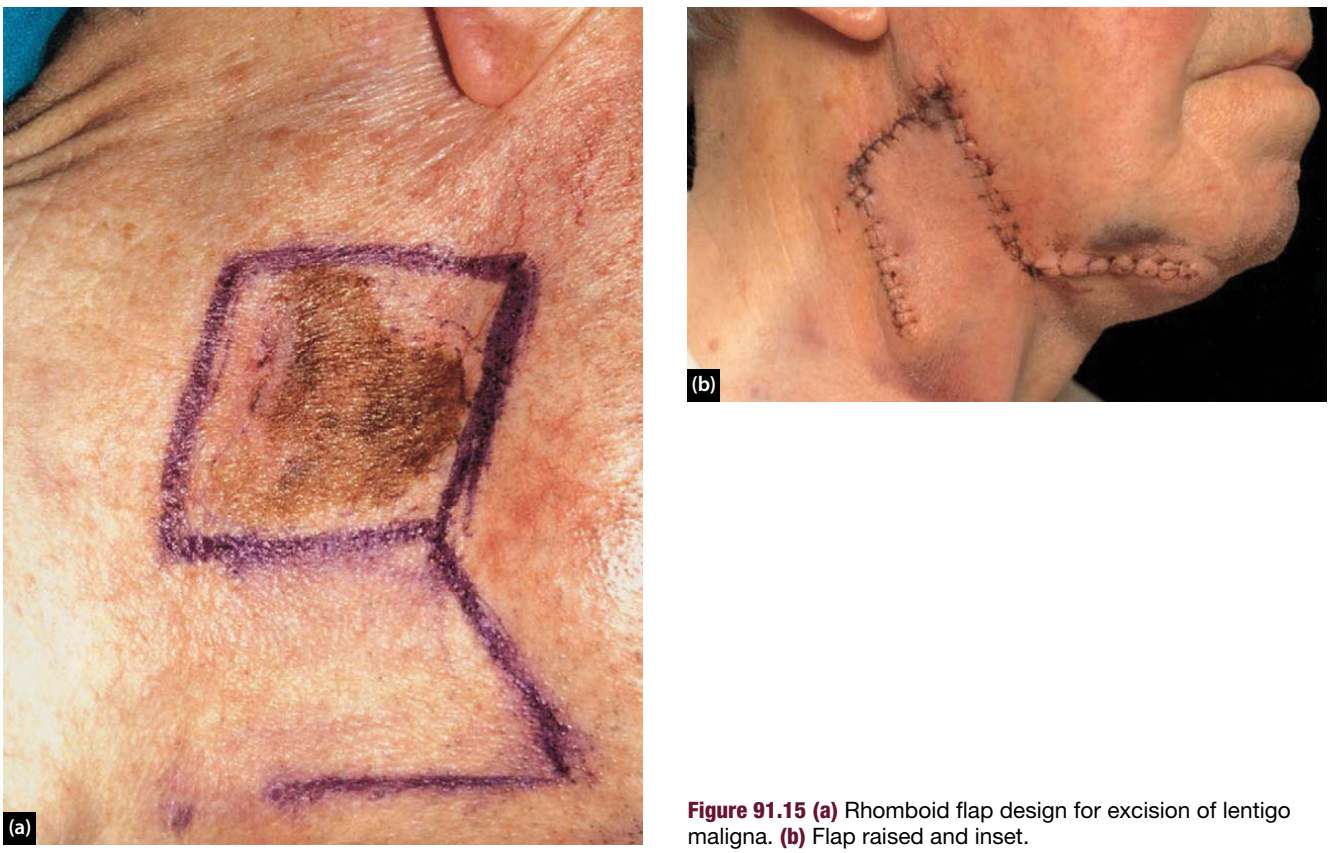


Figure 91.15 (a) Rhomboid flap design for excision of lentigo maligna. **(b)** Flap raised and inset.

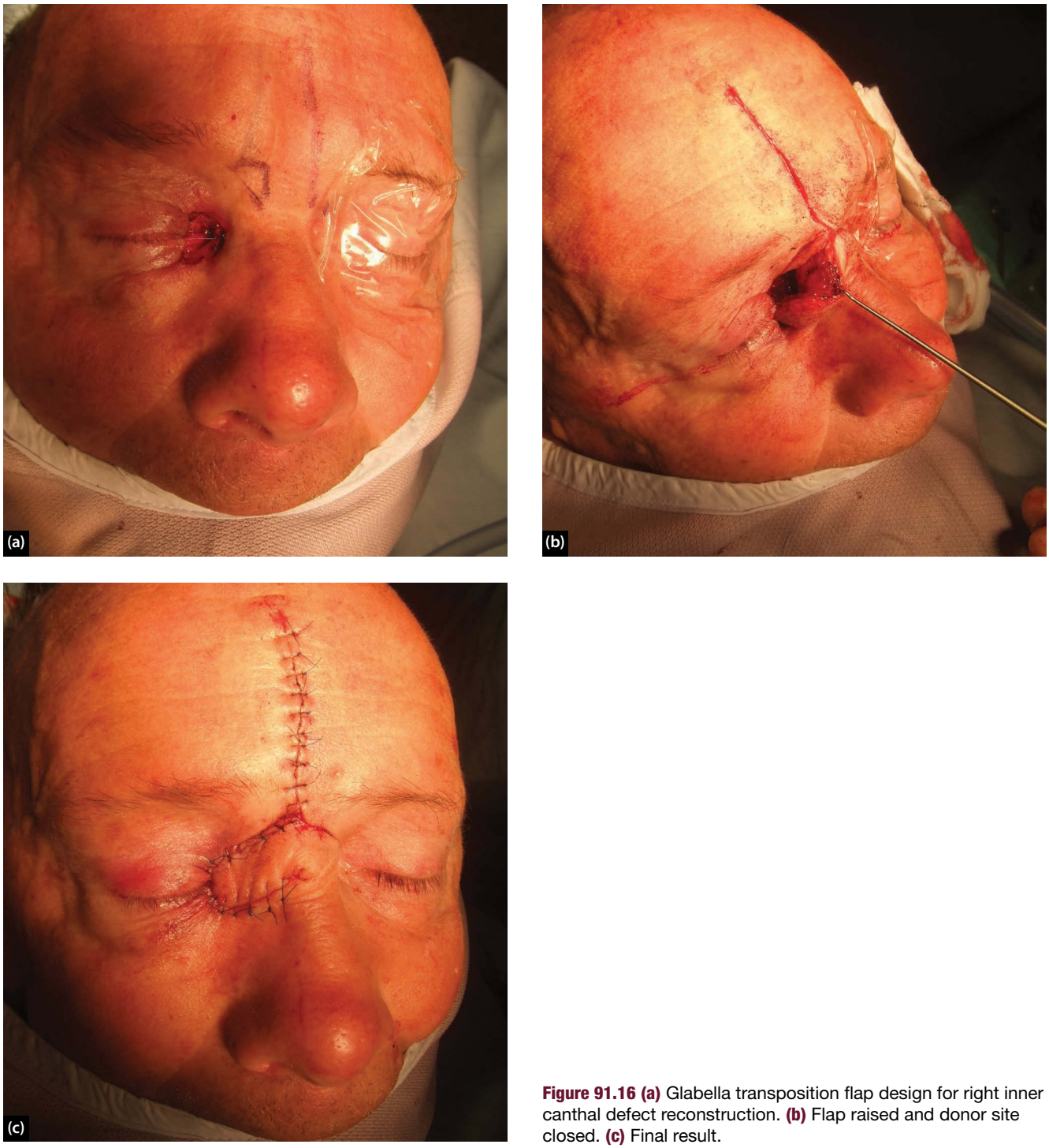


Figure 91.16 (a) Glabella transposition flap design for right inner canthal defect reconstruction. **(b)** Flap raised and donor site closed. **(c)** Final result.

The layer of loose areolar tissue deep to this, also known as the inominate fascia, is an avascular plane. Owing to this, most local flaps of the scalp are raised at this level because it is easy to dissect and relatively bloodless, thus making scalp flaps fasciocutaneous rather than cutaneous. The deepest layer is the pericranium (the periosteum of the skull) which is firmly adherent to the underlying bone. However, it can be raised and turned over on itself to form a pericranial flap.[27] This is viable tissue that can cover exposed bone and is capable of taking a skin graft. Laterally, the pericranium is continuous with the deep temporal fascia overlying the temporalis muscle.

The scalp has a rich blood supply and is supplied by tributaries from the external and internal carotid arterial system. The external carotid branches supplying the scalp include the paired superficial temporal, posterior auricular and occipital arteries. On the anterior scalp, there is further supply from the paired supratrochlear and

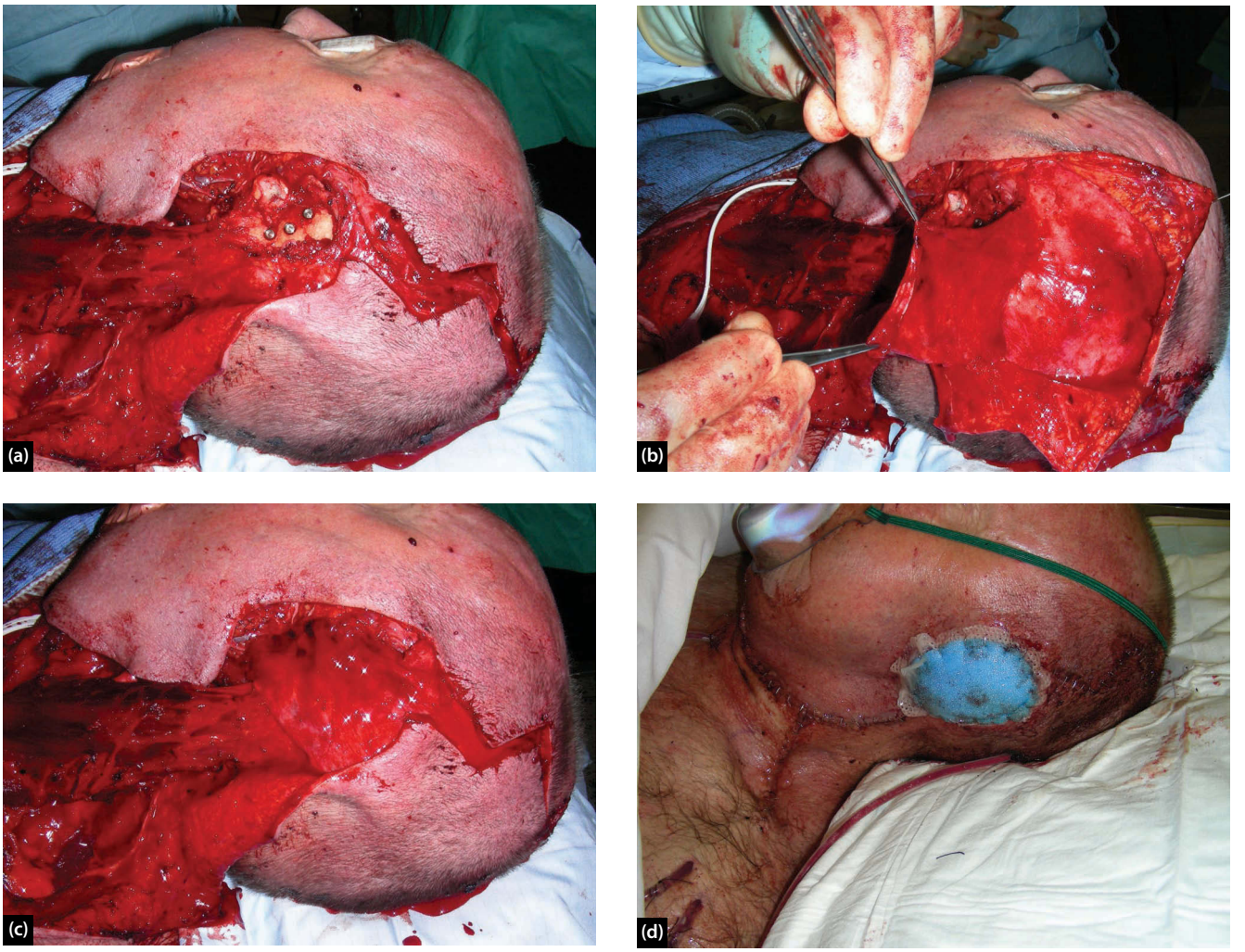


Figure 91.17 (a) Defect in left auricular area with placement of osseointegrated implants. **(b)** Temporoparietal flap raised to cover osseointegrated implants. **(c)** Flap inset. **(d)** Foam dressing covering split skin graft over temporoparietal flap with closure of neck dissection incisions.

supraorbital arteries, themselves being branches of the ophthalmic artery. There is a rich anastomosis between these arteries which allows the entire scalp to survive on any one of these vessels. For the purposes of scalp reconstruction using local flaps, however, it is often convenient to view the blood supply as arising from three separate axes: anterior axis (supratrochlear, supraorbital), lateral axis (superficial temporal, posterior auricular) and a posterior axis (occipital). To allow for reliable vascularity and survival, scalp flaps should contain at least one of these axes.

SCALP FLAPS

There is a paucity of skin and soft tissue on the scalp and therefore only small defects (<3 cm) of the scalp may be closed primarily with undermining. Larger defects require reconstruction with a skin graft, local flaps or free flaps.

Skin grafts are used often on the scalp but require a healthy vascular bed such as the pericranium in order to take. When the ablative surgery includes the pericranium and the outer table becomes exposed, a vascular bed may be achieved either by burring the outer table to expose the small diploic vessels or by covering the exposed bone with a healthy vascular bed such as with a pericranial turnover flap prior to skin grafting.[28] This technique, however, risks dural exposure in children whose cranial bones are thin.

Local scalp flaps can be either rotation or transposition flaps. In order for a rotation flap to be successful, the defect needs to be triangulated and the flap designed large enough to allow coverage of the primary defect and allow direct closure of the donor site. Back cuts or Burow triangles as well as scoring the galea on the underside of the flap can help the flap stretch adequately for closure. A transposition flap on the scalp involves raising a flap adjacent to the defect and transposing it to achieve coverage. This will expose the pericranium over the donor site requiring skin grafting (see **Figure 91.14a**). An alternative is a pericranial transposition flap to achieve a vascularized bed which can subsequently be skin grafted. In larger defects, tissue expansion is a useful adjunct to increase

the amount of tissue available for reconstruction.[29] Alternatively, multiple interdigitating flaps[30, 31] or free flaps can be used; however, this is beyond the scope of this chapter.

TEMPOROPARIETAL FASCIA FLAPS

Scalp flaps can also be useful in reconstructing defects around the head and neck. The fascia in the temporal region is a prime example. This fascia has several well-described layers. The superficial temporal fascia (temporoparietal fascia, TPF) lies immediately deep to the hair follicles and is in continuity with the galea superiorly and the SMAS inferiorly. Deep to this is an avascular layer, known as the innominate fascia, which is in continuity with the loose areolar tissue of the scalp. The deep temporal fascia (or temporalis fascia) is the deepest layer and this is in continuity with the pericranium superiorly.[32] Each of these layers may be used as a local flap to cover defects within their arc of rotation. They are particularly useful in covering exposed bone around the skull (**Figure 91.17**) where a TPF flap is used to cover the exposed temporal bone following total resection of the external ear and extended neck dissection for a $T_4N_1M_0$ cutaneous squamous cell carcinoma.

Forehead and glabella

ANATOMY

The forehead is bounded by the anterior hairline superiorly, the eyebrows inferiorly and the temporal hairline laterally. Underlying the skin is the frontalis muscle which arises as a continuation of the galea aponeurotica and inserts into the dermis of the forehead, allowing brow elevation. It is supplied by the temporal branch of the facial nerve. Sensation to the forehead and vertex of the scalp is supplied by the supratrochlear as well as the superficial and deep divisions of the supraorbital nerve. The superficial division of the supraorbital nerve and the supratrochlear nerve branches lie superficial to the frontalis muscle. The deep division of the supraorbital nerve lies between the galea aponeurotica and the periosteum, medial to and parallel with the superior temporal line of the skull. The blood supply of the forehead is rich and is provided by branches of the internal (supraorbital and supratrochlear arteries) and external (facial and superficial temporal arteries) carotid arteries.

LOCAL FLAPS

The forehead is very visible to observers and so care should be taken to place incisions horizontally or along the hairline and eyebrow. Where direct closure may cause distortion of the hairline or brow, a large full-thickness skin graft would give an adequate result. Larger defects of the forehead can be reconstructed with advancement flaps or hatchet flaps, which are random rotation flaps with a back cut. They can be single or double and heal with minimal scarring. Large defects can be closed using this technique and it is possible to preserve the supratrochlear and supraorbital nerves when dissecting the forehead to maintain sensation.[33] Other techniques for forehead reconstruction include the use of scalp rotation flaps, which can be tissue expanded to produce a larger flap.[34] These, however, are limited as they import hair-bearing skin onto the forehead and distort the hairline.

Eyelid

ANATOMY

The anatomy of the periorbital region is complex and without a good understanding of the structure and function of the eyelids periorbital excisions and reconstructions should not be undertaken. The upper and lower eyelids can be divided into the anterior and posterior lamella in cross section, with an intervening orbital septum. This septum is continuous with the periosteum and extends from the arcus marginalis or the bony margin of the orbit to the margin of the eyelid. In the upper lid, the septum inserts onto the levator aponeurosis 2–5 mm above the superior tarsus whereas, in the lower lid, it attaches to the inferior tarsus directly. The anterior lamella consists of the skin and the orbicularis oculi muscle, whereas the posterior lamella consists of the conjunctiva and the tarsal plates. The skin of the eyelid is the thinnest in the body (1 mm) and is loosely attached to the orbicularis oculi muscle. This muscle is arranged in a concentric ring around the orbit and upon contracture acts as a sphincter, closing the orbital aperture. It can be divided into three parts: an outer orbital part covering bone, and inner preseptal and pretarsal components. Medially, the orbital portion originates directly from the bony orbital rim and the medial canthal tendon. Inferiorly, the orbicularis attaches indirectly to the orbital rim through the orbital-retaining ligament. Laterally, this ligament merges into the lateral orbital thickening.[35] The tarsal plate forms the skeleton of the eyelid and is a dense sheet of fibrous tissue. The superior tarsus measures approximately 10–12 mm vertically from the lid margin; the lower tarsus measures approximately 3.7 mm vertically.[36] The deepest structure of the eyelid is its lining, the conjunctiva, which contains many eccrine and apocrine glands. There are further sebaceous glands of Zeis associated with the eyelashes.

The upper eyelid elevates due to the contraction of the levator palpabrae muscle (innervated by the oculomotor nerve). This originates from the lesser wing of the sphenoid and extends anteriorly along the superior orbit to Whitnall's ligament, which acts as a fulcrum to change its vector of pull from a horizontal to a vertical direction, before finally attaching to the superior tarsal plate. Constriction of the upper eyelid is due to contraction of the orbicularis oculi muscle (innervated by the temporal and zygomatic branches of the facial nerve). The lower lid has only limited descent from the action of the capsulopalpebral fascia, which originates as fibroelastic tissue from the interior rectus muscle and inserts into the inferior tarsal plate. The blood supply of the eyelids consists of a rich anastomosis between branches from the internal and external carotid arterial systems. The sensory supply

of the upper and lower eyelids is derived from branches of the ophthalmic and maxillary divisions of the trigeminal nerve respectively.

EYELID RECONSTRUCTION

Partial-thickness defects

Defects in the eyelid can be partial thickness, with either the anterior or posterior lamella having been excised, or full thickness. Partial-thickness defects of the anterior lamella are best either closed directly if small (up to a third of the eyelid) or resurfaced with a full-thickness skin graft. The posterior lamella can be reconstructed with a graft of buccal or hard palate mucosa[37] or a nasal chondromucosal[38] graft consisting of nasal mucosa and septal cartilage. These grafts are also useful in full-thickness defects.

Full-thickness defects

Reconstruction of full-thickness defects of the eyelids is complex and requires reconstruction of both the anterior and posterior lamella for a satisfactory result. This can be done by using either a single flap to reconstruct both layers or a flap to reconstruct the anterior lamella and a composite graft for the posterior lamella. At least one of the two layers must have its own blood supply as a graft placed on another graft will fail. The size of the defect also needs to be taken into account when planning for reconstruction. Full-thickness defects of up to one-quarter of the lid length can be closed directly and this increases to one-third in the elderly population with lax skin. It is important to note that each of the layers (i.e. conjunctiva, tarsal plate, orbicularis and skin) will need to be repaired individually.

When the size of the defect approaches 50% of the total eyelid, two additional techniques may be used to recruit adjacent lateral tissue to enable closure. The first of these is a lateral cantholysis. A horizontal incision is made from the lateral canthus to the orbital rim. The lateral canthal tendon is identified and divided. The lateral part of the lid can then be mobilized medially to close the wound. The second is by using a tenzel semicircular flap which allows lateral tissue consisting of skin and muscle to pivot on the lateral canthus and advance/rotate into the defect to allow closure.[39] The technique requires a lateral canthotomy, inferior cantholysis and suture suspension of the flap to the lateral orbital margin. This flap is useful in both upper and lower eyelid defects provided some tarsus remains to provide support.

Larger defects of the lower eyelid can be reconstructed with a cheek rotation flap[40] combined with a free composite graft to reconstruct the posterior lamella. Larger defects of the upper eyelid are difficult to reconstruct and usually require a glabellar transposition flap or recruitment of tissue from the lower eyelid in the form of a switch flap[41] or a Cutler-Beard flap.[42] Switch flaps can be based medially or laterally on medial lower eyelid tissue which is then rotated into the upper lid defect. At a second stage, the flap is divided at its base and the donor site is closed with a cheek rotation flap.

The Cutler-Beard flap is an advancement flap from the full thickness of the lower lid, preserving the lower lid margin and tarsus. At a second stage 4–6 weeks later, the flap is divided and returned to the lower border of the intact lower lid margin. The tissue that is left on the upper lid is used to fashion the upper lid margin. These techniques do not import components for the posterior lamella and this will therefore require a suitable graft for reconstruction.

Nose

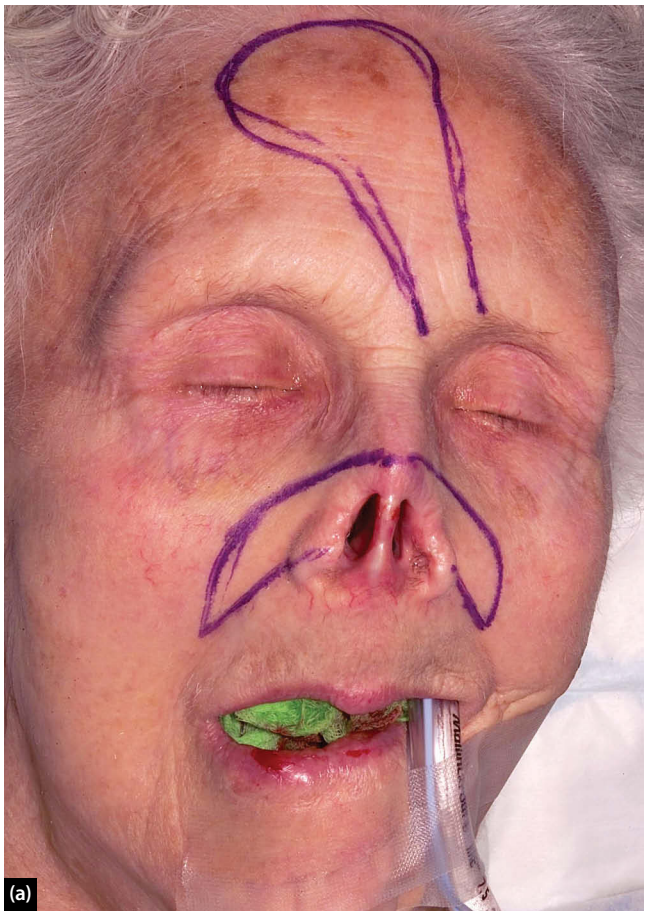
Analysis of the nasal defect to be reconstructed in terms of the component layers is essential when planning reconstruction. Primary closure is limited to small defects due to the relative lack of skin laxity. In partial-thickness defects where there is remaining subcutaneous tissue or perichondrium, the use of full-thickness skin grafts can result in very good cosmetic outcomes. Local flaps are also useful in such cases and will be discussed later. If the defect is full thickness, three distinct layers need to be considered and reconstructed: these are the nasal lining, nasal support and overlying skin. When a small nasal rim defect is being reconstructed, a composite graft taken from the ear which has all three layers is an option. This involves taking a full-thickness piece of the ear including both anterior and posterior skin.

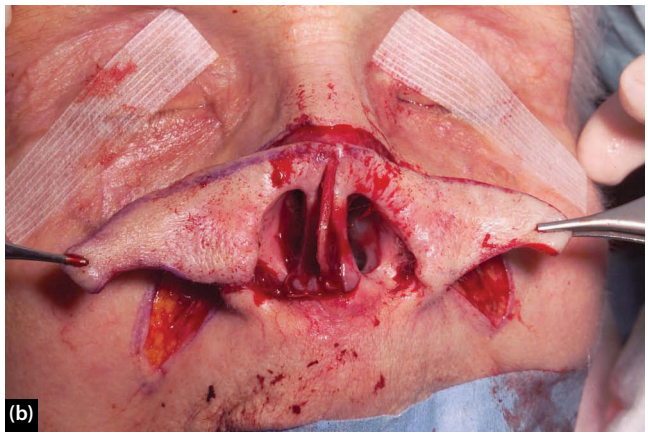
Larger full-thickness defects of the nose following partial or total rhinectomy are more difficult to manage. A local flap can be used to reconstruct both the lining and skin cover of the nose by folding the flap in two. The most commonly used flaps for this are superiorly based nasolabial flaps. Bilateral flaps can be raised to import a large volume of tissue.[43] An alternative to folding a flap is to use one flap for the lining and another for the cover. The nasolabial flap can be used for the lining as can a random hinge flap where adjacent tissue is raised and flipped over to fill the defect.[44] The flaps used as lining can then be covered with either a skin graft or another flap such as a forehead flap (**Figure 91.18**). It has to be remembered that, when dealing with a total rhinectomy defect, very good results can be obtained using a prosthesis. With the advent of osseointegration, a prosthetic nose is both cosmetically acceptable and convenient for the patient.[45] This is a viable alternative to surgical reconstruction.

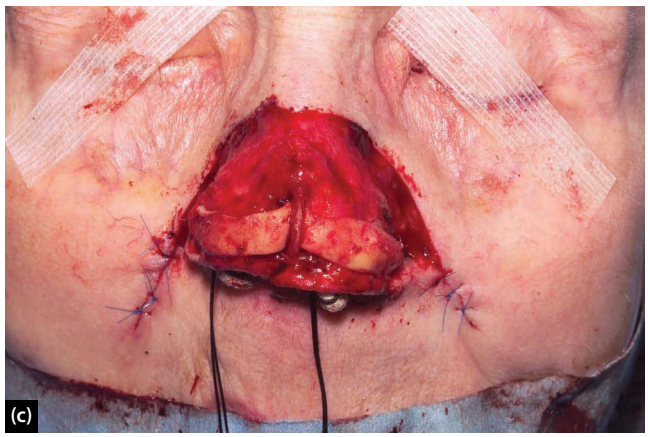
SKELETAL SUPPORT

The nose is supported by a rigid central framework and the more flexible lateral walls composed of the upper and lower lateral cartilages. When lost, it is important to reconstruct these elements to maintain projection and to allow the nasal aperture to remain open to permit airflow. Midline support can be provided by an L-strut, a hinged septal flap, a septal pivot flap or a cantilever bone graft.

An L-strut consists of a longitudinal piece of bone or cartilage that is secured on the nasal radix and extends along the dorsum of the nose to the tip where it is bent







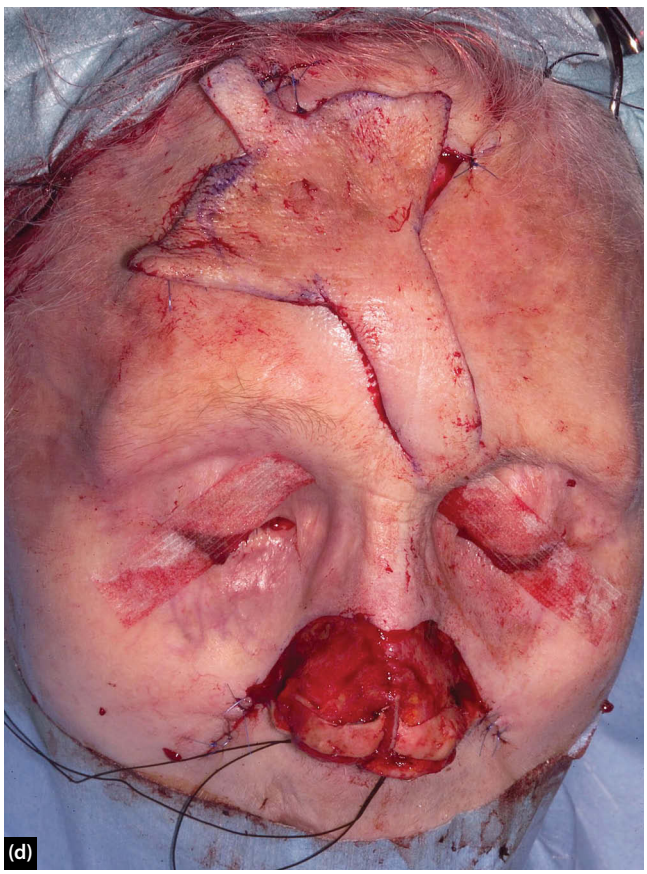


Figure 91.18 (a) Forehead and nasolabial flap design for cutaneous and lining reconstruction respectively. **(b)** Nasolabial flaps raised. **(c)** Nasolabial flaps inset with cartilage grafts to support. **(d)** Forehead flap raised. *(Continued)*

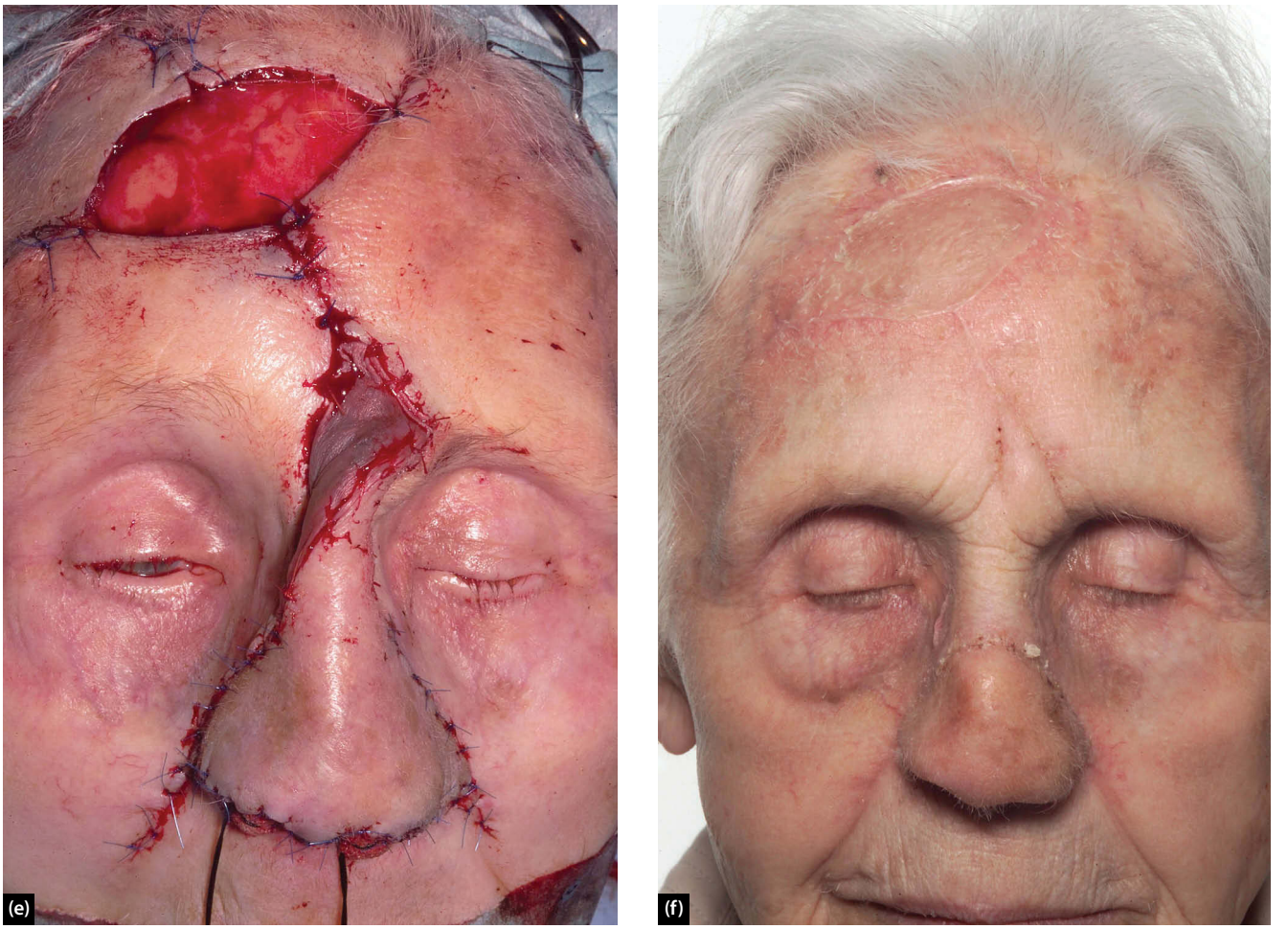


Figure 91.18 (Continued) (e) Forehead flap inset and split skin graft coverage of pedicle and donor site. **(f)** Final result.

sharply to rest on the anterior nasal spine.[46] The hinged septal flap is an L-shaped flap carved from the patient's remaining septum and hinged superiorly on the caudal end of the nasal bones.[47] The septal pivot flap is similar to the hinged septal flap except that the septum in this case brings with it simultaneous mucosa that can be used as lining. If there is insufficient local tissue, then a cantilever graft can be used which consists of a strong, longitudinal bone graft harvested from the calvarium or rib and secured to the radix with miniscrew fixation or wires.[48] The flexible lateral walls of the nose require more pliable cartilage grafts to be used.

LINING

The lining is an important component of the reconstruction as even partial necrosis may result in secondary contracture that will invariably distort the overall result. There are several methods to provide lining. The simplest method is to graft the underside of a flap that is to be used as external cover (e.g. the underside of a forehead flap prior to transfer). When support is also required, a composite graft consisting of skin and cartilage can be used. Local flaps such as the septal door flap,[47] septal mucoperichondrial flap, bipedicled mucosal advancement flap[49] and nasolabial flaps are useful for providing large amounts of tissue for lining. When there is a paucity of local tissue, free flaps such as a free radial forearm flap can be employed to provide lining.

SKIN COVER

The local flap options used to cover nasal defects are varied and choice is dependent on the size and location of the defect. Sidewall defects can be effectively reconstructed with a cheek advancement flap or rhomboid flap.[50] There are a large variety of local flaps that can be used to reconstruct dorsal defects. The glabellar flap[51] transfers tissue from the glabella and is useful in reconstructing defects of the root and upper bridge of the nose. Defects of the dorsum of the nose in the mid and lower third of less than 2 cm in diameter can effectively be reconstructed with the dorsal nasal flap[52] or one of its many variants. These flaps are based on the angular artery and require the nasal dorsum to be degloved to allow sufficient movement prior to flap inset. Advancement flaps such as the Rintala flap[53] are also useful for dorsal nasal defects (see **Figure 91.10**). Other flaps that are commonly used include transposition flaps such as a superiorly based nasolabial flap[54] (see **Figure 91.11**) or a bilobed

flap (see **Figure 91.14**).[55] In addition to these techniques, microvascular free-tissue transfer of a chondrocutaneous flap from the ear has been described.[56]

FOREHEAD FLAP

The forehead flap is a local cutaneous axial flap based on the supratrochlear artery. It is one of the oldest flaps in use and the earliest available description is from 600 BC by Susruta in India.[57] A large flap of skin from the forehead can be raised on this vessel which can then be used to cover defects around the orbit and the nose. The donor site can be the vertical height of the forehead or the flap can be planned obliquely to maximize the length and therefore the reach of the flap. An obliquely placed donor site also reduces the arc of rotation. The donor site can be closed directly if the width of the flap is kept small (less than 2.5 cm) and this leaves minimal scarring. If a wider flap is required, the defect needs to be skin-grafted; an alternative to this is to leave the defect to heal by secondary intention, which can give a very acceptable cosmetic outcome.[58] The transfer is normally carried out in two stages: the flap is raised and the tip of the flap inset into the primary defect. The remainder of the flap is then tubed to form a pedicle. After 3 weeks, the tip of the flap will have undergone some revascularization from the recipient site and the pedicle is then divided and reinset into the secondary defect (see **Figure 91.18d–f**). Alternatively, when reconstructing nasal defects, a third stage can be included.[59] The flap is raised 2 weeks after it is inset, thinned and then reinset. The pedicle is then divided after a further 2 weeks. This prevents having a bulbous nasal tip, giving an overall better cosmetic result.

Lip

The lips are complex structures involved in articulation, swallowing and facial expression. They are three-dimensional structures with an outer layer of skin and an inner layer of mucosa separated by muscle. The junction between the skin and mucosa is a specialized area as the skin blends into white roll, then vermilion and then into mucosa. A 1 mm discrepancy at this junction is noticeable at a distance of 1 metre.

The orbicularis oris muscle contained within the lips is a complex muscle containing fibres in different orientations which can close the mouth, approximate the lips to the maxilla and mandible or purse the lips. In addition, muscle fibres blend into the orbicularis oris from the levator labii superioris and other elevators of the lip superiorly, from buccinators laterally and from depressor labii inferioris and the other lip depressors inferiorly.

The options for donor tissue for lip reconstruction are the remaining lip, the adjacent cheek, the opposite lip or from distant sites. It should be remembered that the goal of lip reconstruction is to restore oral continence, i.e. the role of the mouth as a sphincter, without causing microstomia (a tight or small mouth),[60] and to ensure accurate opposition of the vermilion. The upper and lower lips should be considered separately as different techniques are needed to reconstruct similar defects in the upper or lower lip.

LOWER LIP

Defects up to one-third of the length of the lower lip can be excised as a wedge (or a pentagon) and closed directly. It is important to repair all three layers of the lip, namely the mucosa, muscle and skin, to achieve good function and approximation. Larger, superficial defects of the lip can be resurfaced with a split-thickness skin graft (the entire lower lip can be resurfaced in this way) or by a tongue flap. A flap is raised from the undersurface of the tongue and inset in the defect in the lower lip. The flap is based anteriorly and the donor site is not closed at the time the flap is raised. After 10 days, the flap is divided and inset. At this point the donor site is closed directly.

For defects of three-quarters of the lower lip the Karapandzic flap can be used.[61] This is a combined axial advancement/rotation flap based on the facial artery. A transverse incision from the base of the defect to both nasolabial folds is made and the nasolabial folds are then incised in a cephalic direction. Laterally, the vessels and nerves are identified and preserved. The flap is mobilized by spreading, not dividing, the fibres of the orbicularis oris to preserve its neurovascular supply. The bilateral flaps are then advanced and rotated and then repaired in layers. Total reconstruction of both the upper and lower lip has been described using microvascular free-tissue transfer.[62]

UPPER LIP

Defects up to one-quarter of the size of the upper lip can be closed directly. The orbicularis oris needs to be dissected free of the skin and the mucosa and repaired separately before the overlying tissues are closed. For larger defects, a reverse Karapandzic flap can be used, where the nasolabial folds are incised along with the nasal sill and the skin kept intact in the submental area.

The Abbe flap is a full-thickness flap taken from the lower lip and inset into the upper lip. The layers of mucosa, muscle and skin need to be accurately inset. The flap is then left attached to the lower lip for 1 week before division of the pedicle from the lower lip.[63] The Abbe flap should be taken from the lower lip to reconstruct the upper lip and not from the upper lip to the lower lip. A variation of the Abbe flap is the Abbe-Estlander flap, which is used to reconstruct defects of the oral commisure. It can be taken from either the upper or the lower lip and is a single-stage operation as the pedicle of the flap becomes the new commissure.

Cheek

The cheeks are the largest region of the face. They consist of skin that covers muscle groups which are either attached to the underlying maxilla and mandible or are lined on their inner surface by buccal mucosa. Various important structures transverse the cheeks, including the parotid duct and the branches of the facial nerves. The cheek has

been subdivided into three separate overlapping zones – a suborbital, a preauricular and a buccomandibular area – and reconstruction should follow these regional aesthetic units where possible (see **Figure 91.4**).[64] Consideration also needs to be paid to the 3D structure of the cheek with its natural contours, shadows and hair lines.

TECHNIQUES FOR RECONSTRUCTION

The majority of defects of the cheek will be following ablative surgery for cutaneous malignancies. These normally present in the elderly population and even quite large defects can be closed directly, due to pre-existing skin laxity in this age group. As well as the relaxed skin tension lines, there are other noticeable lines in the cheek in which scars can be hidden. These are the nasolabial fold, infraorbital rim, alar crease, hairline and jawline. Split-thickness skin grafts on the cheek are very noticeable as they tend to transgress the different regions of the cheek and alter the contour and colour, giving a poor cosmetic result. When used in close proximity to the lower eyelid, they may also result in ectropion. For situations where a skin graft is necessary, full-thickness grafts are best to limit contracture and improve colour match. For small defects not amenable to direct closure, local flaps are appropriate. Due to the large surface area of the cheek, a full range of flaps can be utilized, including rhomboid transposition flaps, small cheek rotation–advancement flaps (**Figure 91.19**) or V–Y advancement flaps. Defects that are not amenable to small local flaps may require reconstruction with a cervicofacial flap (**Figure 91.20**).[65] These flaps import tissue from the neck and lower jawline, giving excellent colour, texture and contour match.

In even more extensive defects of the cheek, it may be necessary to import tissue from the chest wall with a cervicopectoral flap.[66] Tissue expansion techniques have also been described and offer excellent colour and texture match[67] but they require at least two stages, multiple visits for expansion and a period of time when the patient will have to tolerate the appearance of the expander.

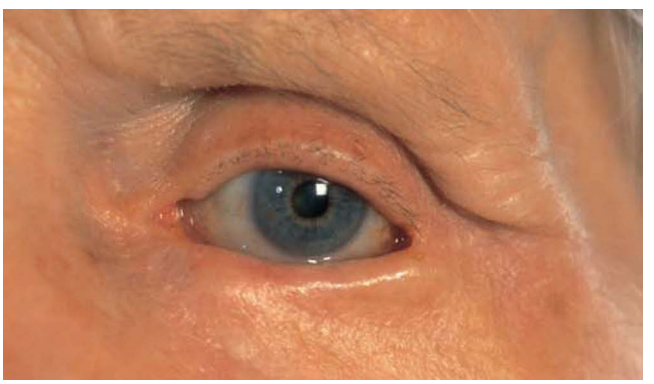
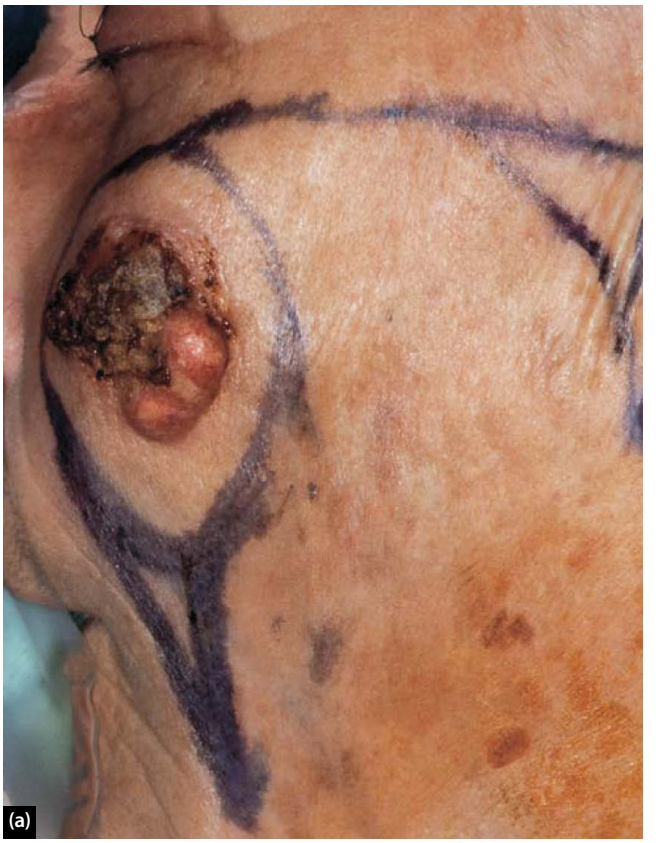


Figure 91.19 Post-operative appearance following lower eyelid reconstruction with cheek rotation flap. This is the same patient as in Figure 91.6.



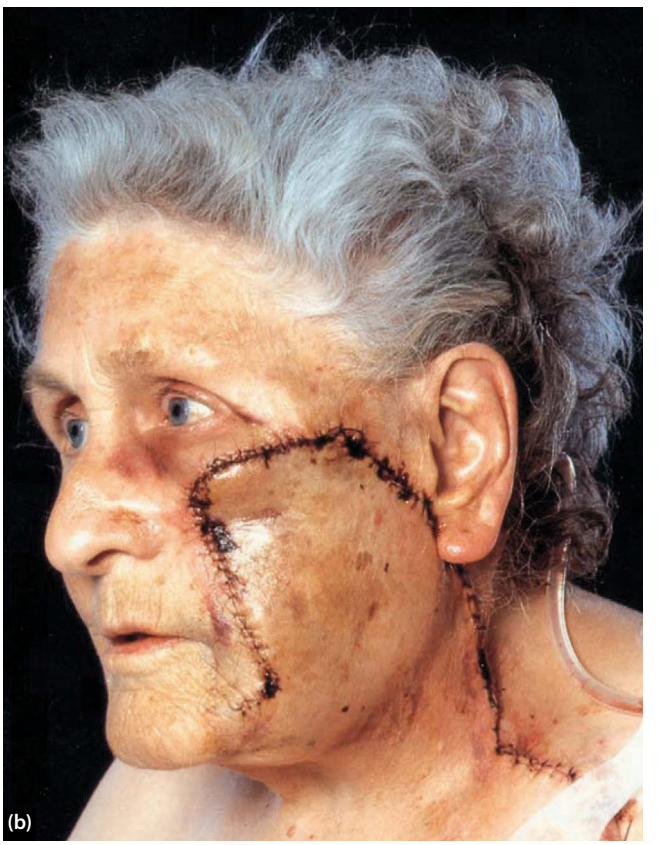


Figure 91.20 (a) Basal cell carcinoma on left cheek marked for excision with cervicofacial flap designed for reconstruction. **(b)** Post-operative appearance following cervicofacial flap reconstruction.

Ear

ANATOMY

The ear consists of skin covering an auricular cartilage framework. The framework comprises the conchal complex, the antihelix–antitragus complex and the helix–lobule complex. The musculature consists of intrinsic (helicis major and minor, tragicus, antitragicus) and extrinsic (anterior, superior and posterior auricularis). Vascular supply is derived from the posterior auricular and superficial temporal arteries with extensive interconnections between the two networks. Sensation is supplied by the great auricular nerve, the auriculotemporal nerve, the lesser occipital nerve and the auricular branch of the vagus nerve.

TECHNIQUES FOR RECONSTRUCTION

The ear is one of the commonest sites for cutaneous malignancies, particularly squamous cell carcinomas, and resection of these tumours may result in partial- or full-thickness defects. Successful reconstruction requires accurate analysis of the defect and a systematic approach to reconstruction. If the defect is small enough, direct closure can be undertaken. Lesions on the upper or middle third of the ear requiring a larger margin for clearance can be closed with a wedge excision. There are various patterns of excision that have been described to decrease tension at the suture line.[68] This technique results in a smaller ear and patients must be warned, but it is well tolerated and usually results in an acceptable cosmetic appearance. Full-thickness skin grafts are useful if the perichondrium is intact or if excision involves either the anterior or posterior skin along with its underlying cartilage. This technique gives a good colour match particularly if the graft is harvested from the head and neck region. If the defect is small but involves the full thickness of the ear, a composite graft from the opposite ear is an option but its survival can be tenuous.

There are also various local flaps that can be employed. An Antia–Buch chondrocutaneous advancement flap is useful for small to moderate sized defects of the upper and middle ear.[69] This involves freeing the helix from the scapha through an incision in the helical sulcus extending through the anterior skin and cartilage. The posteromedial skin superficial to the perichondrium is undermined, and the superior and inferior chondrocutaneous components are advanced for closure.

Another reconstructive option for the upper ear is a conchal rotation flap, which involves the rotation of the full thickness of the concha on the external edge of the ear to form the new superior ear.[70] The Converse tunnel technique involves the insertion of a cartilage graft shaped to the size of the defect beneath the mastoid skin, which is then sutured to the edges of the defect. At a second stage, the auricle is separated from the mastoid area with the graft attached and the donor site is skin-grafted.[71]

For large defects of the middle ear, reconstruction can be undertaken as described by Dieffenbach.[72] This involves a postauricular advancement flap which is approximated into the defect. A cartilage graft can be used as support beneath the flap. At a second stage, the flap is divided at its base and folded around the posteromedial aspect of the ear to complete the reconstruction. A skin graft is applied to close the donor defect. Techniques for reconstructing defects of the lower third of the ear are limited. A double-lobed postauricular flap may be used to reconstruct the earlobe. It is raised and folded onto itself, then sutured onto itself and remaining auricle to form the new earlobe.[73]

KEY POINTS

- Make use of the reconstructive ladder.
- Understand the process of wound and graft healing.
- Replace like with like.
- Reconstruct individual cosmetic units where possible.

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CHAPTER 92

PEDICLED FLAPS IN HEAD AND NECK RECONSTRUCTION

Ralph W. Gilbert and John C. Watkinson

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SEARCH STRATEGY

Data in this chapter may be updated by a Medline search using the keywords: pedicled flap, head and neck, temporoparietal flap, FAMM flap, submental flap, nasolabial flap, pectoralis major flap, latissimus dorsi flap, trapezius flap.

INTRODUCTION

Defects following head and neck surgery can often be closed by direct suture. This applies to both the skin and mucous membranes. This technique is used when the defect is small, and where local conditions allow adequate amounts of mobile tissue. However, for larger defects or in situations when direct suture is not applicable, surgical defects may be filled by free grafts, local skin flaps, with pedicled flaps that may be either axial cutaneous or musculocutaneous, or with free tissue transfer. This chapter outlines the use of pedicled flaps in head and neck surgery.

GILLIES' PRINCIPLES OF RECONSTRUCTIVE SURGERY

There are some simple rules to head and neck reconstruction. These are well summarized by some of the commandments of Sir Harold Gillies[1] that relate to reconstruction in general:

- Losses must be replaced in kind.
- Treat the primary defect first.
- Thou shalt provide thyself with a lifeboat.
- Thou shalt not throw away a living thing.
- Replace things into their normal position by recreation of the defect.

Reconstructive techniques can be used effectively as building blocks, either singly or in combination, to reconstruct the defect. However, before they are described in detail, it is important to understand in general terms how they work. The many and varied clinical situations in which they may be used are discussed in those chapters that relate to the resection of the specific tumour in question (i.e. Chapter 12, Oral cavity tumours including the lip and Chapter 13, Oropharyngeal tumours).

TYPES OF FLAP

There are a number of different types of flap that maybe used in head and neck reconstruction. These are:

- local flaps:
  - random
  - axial pattern
- distant axial:
  - deltopectoral
  - cervical
  - occipitomastoid
- myocutaneous:
  - pectoralis major/latissimus dorsi
- free tissue transfer.

Distant axial and myocutaneous pedicled flaps are used less and less in head and neck reconstruction following the introduction of free tissue transfer. However, they do have a number of uses in certain situations for soft tissue

TABLE 92.1 Advantages and disadvantages of pedicled flap transfer

Advantages	Disadvantages
• Relatively straightforward to raise • Reliable • Adequate blood supply • Can be used as 'life boats' for salvage surgery • Useful in the presence of infection	• Bulky • Cannot be tubed • May be associated with significant donor site morbidity • May represent a compromise balancing the ideal reconstruction and the surgeon's skill set

reconstruction and their advantages and disadvantages are shown in **Table 92.1**.

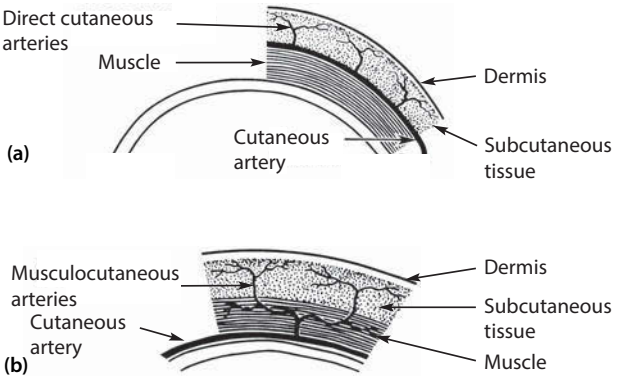

Figure 92.1 Blood supply of axial and random flaps. (a) Note that the axial flap is based on an arteriovenous pedicle that runs within the skin superficial to the underlying muscle layout and parallel to the overlying skin. **(b)** This differs from a random flap.

AXIAL FLAPS

An axial flap is based on a named arteriovenous pedicle that runs within the skin superficial to the underlying muscle layer, parallel to the overlying skin (**Figure 92.1**). Axial flaps have an extremely good blood supply that is determined not only by their length and breadth ratio but also by the vascular territory of the vessels that supply them. Because of this, they can generally be raised to a much greater length than random flaps and can therefore be used to move skin over a greater distance. The use of these flaps in the 1960s was the first major step in head and neck reconstruction. Their routine use has largely been superseded by musculocutaneous and free tissue transfer, but the deltopectoral flap still has a role in head and neck surgery.

Forehead flaps

The forehead flap is an axial flap that provides large areas of skin and subcutaneous tissue that may be used to reconstruct defects below the level of the eyes. In its original form (as described by McGregor and McGregor),[2] the axial forehead flap based on the anterior branch of the temporal artery was one of the first flaps used in intraoral reconstruction. It is rarely used today as it leaves a disfiguring donor site and there are better alternatives. It does represent a potential lifeboat for a failed myocutaneous or free tissue transfer in oral or oropharyngeal reconstruction. When used for oral cavity reconstruction, it is passed into the oral cavity medial to the zygomatic arch. The temporalis muscle tendon must be divided from the coronoid process to facilitate access.

The most commonly raised forehead flap is the cutaneous axial median forehead flap, based on the supratrochlear artery. It can be raised and transposed to reconstruct areas in the upper medial cheek region and any defect of the external nose (**Figure 92.2**). The donor site will often close primarily and the cosmetic result is excellent. Where larger areas of tissue are required, for example in complete nasal resurfacing, larger forehead flaps may be designed (e.g. Millard flying seagull flap), which may be facilitated by prior tissue expansion to ease donor site closure. Controversy exists regarding the use of tissue expansion to achieve primary closure. Some authors believe that the expanded forehead flap contracts excessively when used for nasal reconstruction, compromising the ultimate reconstructive result. Additionally the defect on the scalp when left to close with secondary intention often produces an excellent aesthetic result with normal contour and skin colour. These techniques are best suited in patients with high foreheads with some lax tissue to facilitate primary closure.

Nasolabial flaps

The nasolabial flap was first documented in the Indian Sushruta of 600 BCE and has been a workhorse for reconstruction of defects around the face and the anterior oral cavity. The artery is based on distal branches of the facial artery and its venae commitantes. The flap is usually designed with an inferior base, but can be based superiorly with a more random vascular supply. The design usually places the most medial limit of the flap in the nasolabial fold with the superior limit approximating the medial canthus of the eye. The medial to lateral dimension of the flap is determined by the defect to be reconstructed and the ability to primarily close the donor site. Flap elevation is usually initiated distally with a retrograde dissection above the plane of the facial musculature. In the intraoral application a tunnel is placed traversing the facial muscles and buccinators, allowing the inferiorly based flap to enter the oral cavity (**Figure 92.3**).

This flap is extremely reliable when based inferiorly, with a relatively inconspicuous donor site, particularly when bilateral flaps are used. Its greatest application intraorally is for the anterior floor of mouth and gingiva, where its use is both simple and effective. The donor site for this flap is best tolerated in elderly patients with rhytids that mask the donor site.

Submental island flaps

This flap, first described by Martin in 1983,[3] has great utility as an axial pattern flap or a free flap for reconstruction of the facial skin or intraoral lining. The flap is supplied by a branch or branches of the facial artery that pass

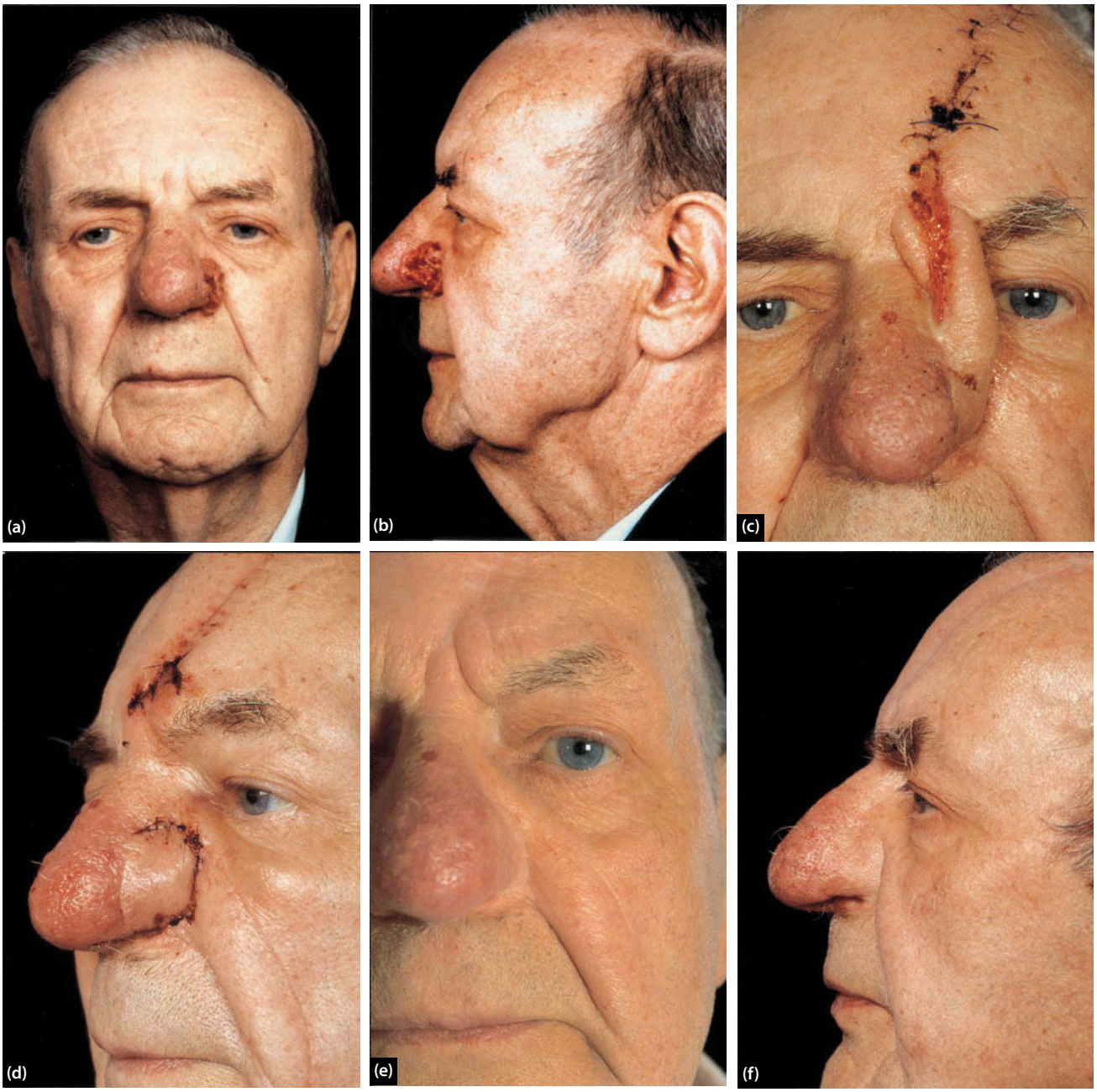

Figure 92.2 Use of a midline forehead flap to repair a defect in the lower left aspect of the nose and cheek. (a, b) A patient with a T4 basal cell carcinoma of the lower aspect of the nose and medial part of the cheek. **(c)** Wide excision was achieved, repair of the lateral side of the nose was with an infolded delayed forehead flap and the cheek was repaired using V to Y advancement. **(d)** The forehead flap was divided 3 weeks later. **(e, f)** The final result.

either over or through the submandibular gland, traversing medially on the mylohyoid muscle and then deep to the anterior belly of the digastric muscle to provide a perforator-based arterial supply and venous drainage to the submental skin.[4] The flap has a variable venous drainage via the facial vein. There can be occasional problems with venous congestion, particularly in the reverse flow design, because of valves in the facial vein. The flap is usually designed in the midline, just below the margin of the mandible, with the superior/inferior dimension determined by the ability to close the submental skin (**Figure 92.4**). Dissection is usually initiated on the contralateral side to the planned vessel pedicle. Skin and subcutaneous tissues are incised down to the level of the investing fascia of the digastric muscle, with the plane of dissection carried in the submental triangle at the level of the mylohyoid muscle. The ipsilateral anterior belly is usually divided distally and proximally to preserve the blood supply to the flap and the dissection proceeds in a retrograde fashion to the facial artery and vein. The flap can be tunnelled under the mandible and through the submandibular and submental space for oral reconstruction, or can be rotated or transposed onto the face for soft tissue coverage. The unique advantage of this flap is its colour match with

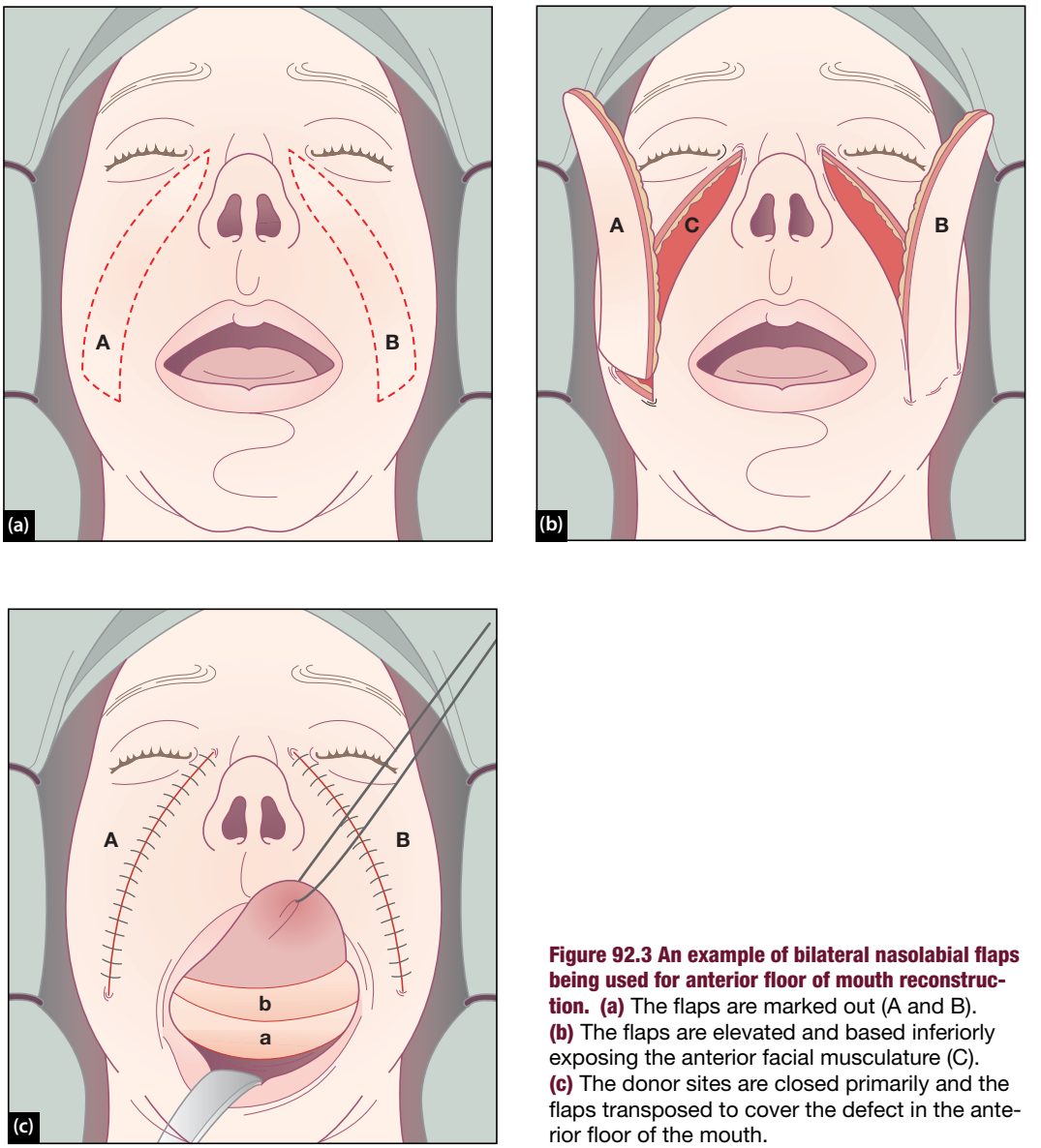

Figure 92.3 An example of bilateral nasolabial flaps being used for anterior floor of mouth reconstruction. **(a)** The flaps are marked out (A and B). **(b)** The flaps are elevated and based inferiorly exposing the anterior facial musculature (C). **(c)** The donor sites are closed primarily and the flaps transposed to cover the defect in the anterior floor of the mouth.

facial skin and the relative inconspicuous nature of the donor site scar. There have been reports of problems with venous congestion, particularly when tunnelled through the submandibular space.

Facial artery myomucosal flaps

The facial artery myomucosal flap (FAMM) was first described by Pribaz et al. in 1992.[5, 6] This flap is composed of oral mucosal and buccinator muscle and is based on branches of the facial artery. The anatomy of this flap is based on the buccinator muscle and its relationship to the facial artery. The buccinator is covered medially by the submucosa and mucosa and laterally by the external lamina of the muscles of facial expression, the masseter, the buccal fat pad, and the facial artery and vein.

The facial artery, a branch of the external carotid artery, enters the face by curving around the lower border of the mandible at the anterior edge of the masseter muscle. It then follows a tortuous course, passing superiorly and anteriorly to a position just lateral to the commissure of the mouth. At this point it lies deep to the risorius, zygomaticus major muscle and the superficial lamina of the orbicularis oris muscle. It lies superficial to the buccinator muscle and the lateral edge of the deep lamina of the orbicularis oris muscle. At this point in its course it gives off multiple perforating vessels to the cheek and the superior labial artery. It continues superiorly to the angular artery, which reaches the medial canthus. It has communicating branches with the buccal and infraorbital branches.

The FAMM flap is an axial pattern flap based on the facial artery. The flap may be harvested as an inferiorly based flap based on antegrade flow or a superiorly based flap with retrograde flow. The basic harvest technique is to Doppler out the facial artery through the buccal mucosa and map the course of the vessel. For the inferiorly based flap, dissection begins anterosuperiorly to identify the arterial supply to the upper lip with division of the facial

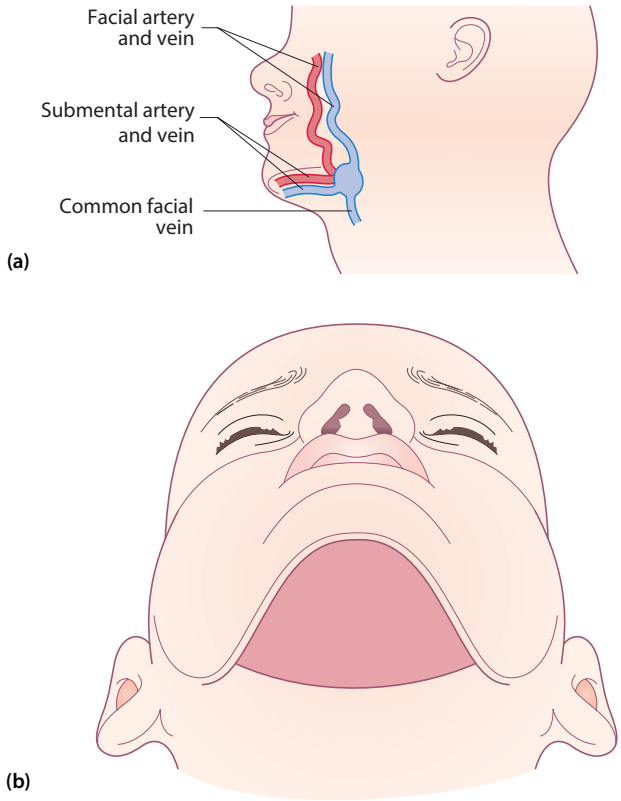

Figure 92.4 **(a)** The submental island flap is pedicled on branches of the submental artery and vein; **(b)** the size of flap available.

artery at this point and then retrograde dissection, which includes the mucosa, buccinator, facial artery and the tissue and venous plexus that lies between the artery and the muscle. In the superiorly based flap, the dissection begins inferiorly with visualization and ligation of the facial artery and then a retrograde dissection of the tissues including the buccinator muscle. A flap of 7–8 cm can be harvested with a thickness of 8–10 mm.

The FAMM flap is ideally suited for reconstruction of small mucosal defects in the oral cavity and in particular the mucosa of the lip. The flap can also be rotated across the alveolus to close small defects of the floor of mouth or tongue, as well as the palate.

Temporoparietal fascial flaps

The temporoparietal flap is a versatile local rotation or free fascial flap for reconstruction of the head and neck or extremities. The flap was first described by Golovine in the 19th century for orbit reconstruction. More recently it has been popularized by Brent and Byrd,[7] and others, for microtia repair and auricular reconstruction. Its unique characteristics are a remarkably robust vascular supply with a very thin and pliable flap with minimal donor site morbidity.

The arterial supply of the temporoparietal flap is the superficial temporal artery, a terminal branch of the external carotid artery. The vessel classically has a number of branches above the zygoma, with most patients

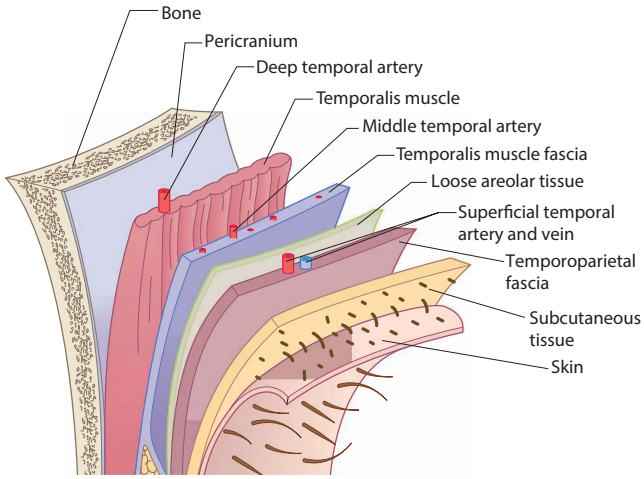

Figure 92.5 The different layers of the scalp, with particular reference to the position of the temporoparietal fascia.

having a prominent frontal branch and dominant branch that ascends towards the vertex of the skull. The venous drainage is via the superficial temporal vein running with the artery. There is some variation in venous anatomy, with a small percentage of patients having venous drainage through the post-auricular vein or occipital veins. The temporoparietal fascia (TPF) lies just under the subcutaneous tissue of the lateral scalp (**Figure 92.5**). The fascia has an inner and an outer layer, with the artery and vein entering between the inner and outer layers and then coursing vertically in the outer layer of the fascia. The outer layer of the TPF extends as the superficial muscular aponeurotic system (SMAS) below the zygoma. A thin muscular layer (the superficial auricular muscle) separates two parts of the outer layer of the fascia below the temporal line. The inner layer of the TPF contains a dense vascular network, which originates from the outer layer. Two nerves have an anatomic relation to the flap: the auriculotemporal nerve, a branch of V3, lies within the superficial layer of the TPF and theoretically could provide for a sensate flap; and the frontal branch of the facial nerve traverses over the zygoma in the same plane as the frontal branch of the superficial temporal artery and can be injured if the dissection is carried too far forward in the plane of this vessel.

For flap harvest the patient is usually positioned in the supine position, with the drape line along the vertex of the scalp leaving the post-auricular area exposed.

The important landmarks for this flap are the arch of the zygoma, the pinna and the usual landmarks of the facial nerve. The artery usually lies just in front of the pinna and is easily palpated or detected with the Doppler in the this location. The artery ascends vertically to the apex with a frontal branch coming off 1–3 cm above the zygomatic arch. The flap is harvested as an elliptical or teardrop shape, above the level of the zygoma. The incision is placed just posterior to the position of the vertical branch and can be either a straight or curvilinear incision into the scalp or 'Y' shaped for larger teardrop-shaped flaps. The inferior limit of the incision is usually the tragus but inferior extensions can be used for extended rotations or if the surgeon

wishes to visualize the facial nerve. The initial incision is started just above the zygoma, extending into the scalp. The surgeon harvesting this flap for the first time must take great care not to incise too deeply as the pedicle can easily be divided during the incision. The plane of dissection is initiated by defining the level of the superficial temporal fascia just below the subcutaneous fat layer in the scalp. A good landmark is to look for the hair follicles; if they are being transected, the surgeon is elevating the flap too superficially. Once fully mobilized from the overlying skin, the flap is incised around its periphery and elevated in the plane just above the temporal fascia. Dissection is carried down to about 2 cm below the arch of the zygoma to ensure an appropriate arc of rotation (**Figure 92.6**). Clinical applications for this flap include: orbital reconstruction, including the extenteration cavity; upper and lower eyelids and the eyebrow as a fascio-cutaneous hair bearing flap; auricular reconstruction, including microtia and traumatic or oncologic deformities; palate reconstruction; and buccal mucosal reconstruction.

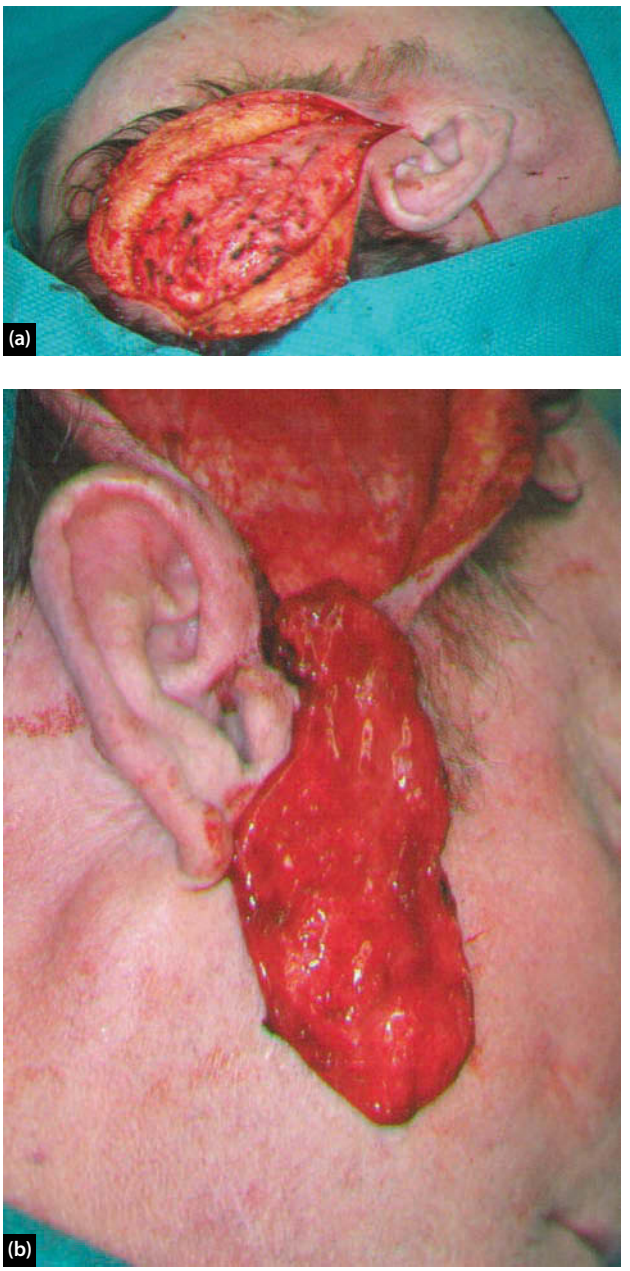

Figure 92.6 (a) Donor site of the temporoparietal flap. **(b)** Arc of rotation temporoparietal flap.

DISTANT AXIAL FLAPS

Deltopectoral flaps

This flap was described by Bakamjian and Littlewood in 1964[8] and is an axial pattern flap designed on the anterior chest wall between the line of the clavicle and the level of the anterior axillary fold. Its vascular supply arises from the upper three or four perforating branches of the internal mammary artery that emerge through the medial end of the intercostal spaces (**Figure 92.7**). Its boundaries are the clavicle superiorly, the acromium laterally and a line running through the anterior axillary fold to above the nipple inferiorly. The flap will extend to any site in the neck and occasionally up to the level of the zygoma. This flexibility is explained first by the fact that it retracts from side to side after it has been elevated, and not from end to end, so that it may elongate slightly over time, particularly in patients over 60 years of age. Second, its flexibility is due to an anomalous pivot point (see 'Planning the transfer' below).

The territory of the perforator vascular system has been shown to extend as far as the groove separating the deltoid from the pectoralis major (deltopectoral groove). Any extension of the flap beyond this should not be regarded as an axial pattern flap. One must be aware that any extension of the flap beyond this area may result in failure of the tip of the flap.

The flap is marked out using the landmarks described above and then elevation begins laterally. The pectoral

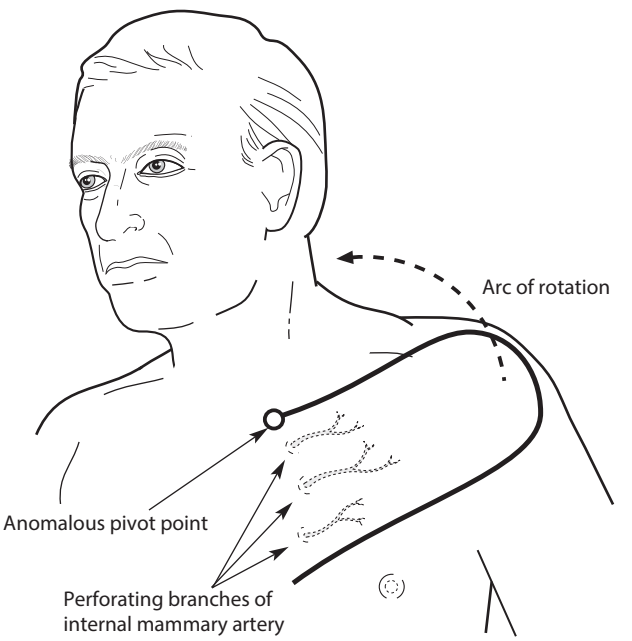

Figure 92.7 Design and planning of the deltopectoral flap. Note the position of the anomolous pivot point at the upper medial end of the flap.

fascia is left on the flap, leaving the muscle fibres below absolutely bare. Any branches of the acromiothoracic axis that are encountered should be ligated. Monopolar diathermy is used judiciously on the flap and the muscle, as this could damage the flap and any diathermy marks on the muscle may compromise the subsequent take of any skin graft. When raising the flap, retraction is upwards by an assistant using skin hooks; it must not be doubled back on itself as this could lead to buttonholing.

PLANNING THE TRANSFER

The deltopectoral flap has an anomalous pivot point. There is considerable laxity of the skin on the anterior axillary fold when the arm is abducted. This means that the lower border of the flap is considerably longer than the upper part. The pivot point on the flap is thus at the medial end of the upper limb and not the lower limb. This needs to be taken into account when planning the flap. The donor site is usually covered with a split skin graft. The uses of a deltopectoral flap are:

- to allow a one-stage reconstruction of the anterior neck skin
- to reconstruct a defect by passing as a bridge over normal; once take has occurred over a period of 3 weeks, the pedicle is divided and the remaining part of the flap may be returned to the donor site or discarded
- to reconstruct large defects on the lower face and upper neck. The pedicle may be inserted into part of the defect to facilitate take and then the pedicle is divided inferiorly and the flap inserted into the rest of the lower defect. This is analogous to 'waltzing'. The deltopectoral flap may also be used in the repair of a pharyngeal fistula but usually muscle bulk is required with the skin, and therefore other flaps are preferable.

Supraclavicular artery island flaps

The supraclavicular artery island flap (SAI) is a local fasciocutaneous flap harvested from the skin on the shoulder and supraclavicular area. This flap was first described in 1979 by Lamberty,[9] who described a supraclavicular artery flap based on a branch of the tranverse cervical artery in the majority of cases with occasional supply from the suprascapular vessels. Pallua et al.[10] expanded the anatomic knowledge of this flap, demonstrating that the flap in all cases was supplied by a branch of the transverse cervical artery with venous drainage via paired venae commitantes joining either the external jugular vein or the transverse cervical vein. They described the take-off of the artery within a triangle bounded anteriorly by the posterior border of the sternocleidomastoid muscle, posteriorly by the external jugular vein and inferiorly by the clavicle (**Figure 92.8**). Pallua demonstrated that flaps up 30 cm in length and 12 cm in width could be harvested and rotated into head and neck defects. Chiu et al.[11] in 2009 reported an initial experience with this flap in oncologic defects of the head and neck and since that time numerous authors have reported experiences with this flap.

FLAP HARVEST

The supraclavicular artery is identified using a hand-held Doppler, usually originating in a triangle bounded anteriorly by the posterior border of the sternocleidomastoid muscle, posteriorly by the external jugular vein and inferiorly by the clavicle. The vessel is followed out over the clavicle to identify the axis and design of the flap. The flap is usually designed with a width of 6–7 cm and a length of 20–25 cm from the rotation point. Dissection starts distally and is carried subfascially over the deltoid until one reaches the anterior border of the trapezius. The spinal accessory nerve is identified and dissection continues in a subfascial plane. The dissection then turns to elevation of the infraclavicular portion of the flap in the subfascial plane; this dissection in the subfascial plane is maintained until over the clavicle. Once the acromion is reached the dissection is continued with careful dissection, with branch ligation with either bipolar cautery or surgical clips. Skeletonization of pedicle is not usually necessary, unless wider arcs of rotation are required. The distal extension of the transverse cervical artery may restrict rotation and

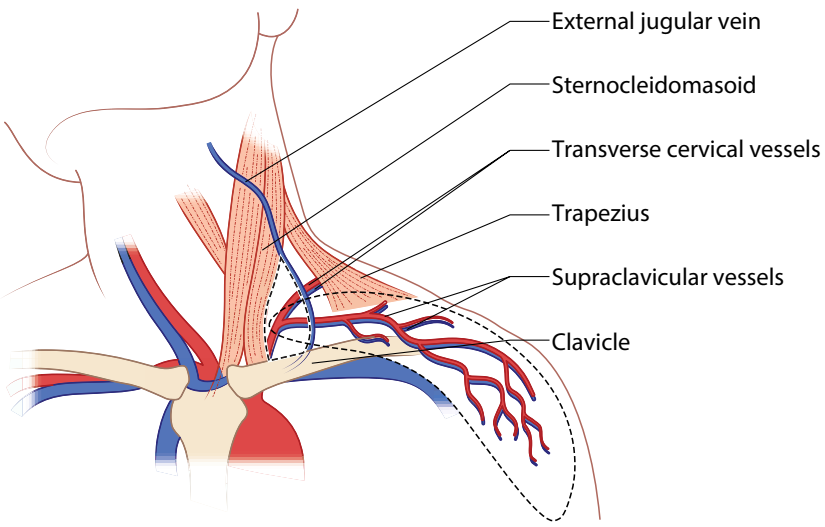

Figure 92.8 Supraclavicular artery island flap.

can be ligated if necessary. The proximal portion of the flap is usually de-epithelialized to allow tunnelling into a facial or intraoral defect.

CLINICAL APPLICATIONS

The SAI flap has broad application for external skin defects extending from the base of the neck to the parotid. In addition, numerous authors have described its use for oral and oropharyngeal defects. The advantages of the flap are the ease of elevation and a neck donor site. Rates of venous congestion and flap failure vary in the literature, but are likely much higher than those experienced with classic free tissue transfer.

OTHER DISTAL AXIAL CUTANEOUS FLAPS

These include other cervical skin flaps and occipitomastoid-based flaps.

Cervical-facial skin flaps of varying shape, size, site and direction may be designed to make good use of lax neck skin for reconstructive purposes. In general, they make use of the side of the neck. They are most frequently used as a primary or salvage procedure for external skin defects of the lower face and cheek. This flap has the unique advantage of providing excellent if not identical colour match for external defects. The nape of neck (Mütter) or posterior scalp flap is a random pattern skin flap that exploits the neck skin over the trapezius muscle and can be raised on the occipital vessels and extended downwards to the spine of the scapula. It may be swung on its upper pedicle to reconstruct areas in the lower face and submandibular region.

Myocutaneous and muscle-only axial distant flaps

One of the most important discoveries in the last 30 years is that the skin over most parts of the body receives its blood supply from small musculocutaneous arteries (perforating vessels) that enter it from the underlying muscle (**Figure 92.9**). It subsequently became apparent that an obvious way to move a large area of skin for reconstructive purposes was to transpose the skin with its underlying muscle vascularized by its dominant blood supply:

- pectoralis major
- latissimus dorsi
- sternomastoid
- trapezius
- platysma.

The pectoralis major and the latissimus dorsi flaps represent the workhorses for many head and neck reconstructive surgeons and a detailed understanding of the anatomy and harvest techniques will be a significant asset to the head and neck surgeon.

The muscles are supplied ultimately by segmental vessels that have similar perfusion pressures to the aorta. They run deep within the muscle and give off perforators that enter the muscles and provide communication between the segmental vessels and the musculocutaneous vessels in the skin. There may be several arterial pedicles. The artery is usually accompanied by two venae commitantes that unite after leaving the muscle to drain into a major regional vein. Five types of muscular arterial supply have been described (**Table 92.2**).

The blood supply to the muscles may also be random or axial in pattern. Most of the round muscles, for example the sternomastoid, have a random supply: perforators penetrate the belly at one end and immediately break up into small branches. The flatter muscles such as pectoralis major and latissimus dorsi have an axial supply: the major arterial supply runs the whole length of the deep surface of the muscle, giving off perforators as it goes.

Essential surgical points are:

- With the axial muscular flaps, although the blood supply to the muscle is axial, the blood supply of the skin upon the muscle is random.
- There is a minimum size of skin paddle that should be taken to ensure that one incorporates enough perforators

TABLE 92.2 Patterns of vascular anatomy

Vascular pedicle		Examples used in head and neck surgery
I	One pedicle	None
II	Dominant pedicle and minor pedicles	Sternocleidomastoid Trapezius Platysma
III	Two dominant pedicles	Temporals
IV	Segmental pedicles	None
V	One dominant pedicle plus secondary segmental pedicles	Pectoralis major Latissimus dorsi

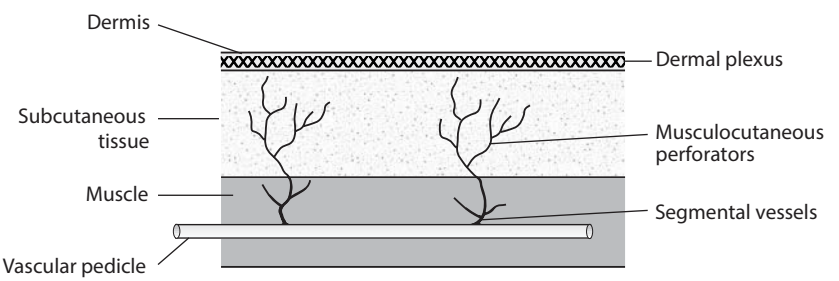

Figure 92.9 Blood supply to a myocutaneous flap.

to supply the skin flap. For pectoralis major and latissimus dorsi flaps, this usually means a skin paddle measuring 5×3 cm (the size of the palm of an adult's hand).
- Smaller skin paddles may not survive.

Pectoralis major flaps

This flap was first described by Ariyan in the late 1970s.[12, 13] The muscle's origins are the clavicle, the sternum and slips from the upper seven ribs. There is also a variable origin from the aponeurosis of the external oblique, which is variable in size. It is inserted into the bicipital groove of the humerus. The muscle has three major segmental sub units: clavicular; sternocostal; and an external segment (the most lateral part of the muscle), which originates from the ribs.

The main arterial supply, which provides the vascular basis for this flap, comes from the pectoral branch of the acromiothoracic artery that arises from the first part of the axillary artery (**Figure 92.10**). The pectoral branch of the acromiothoracic axis emerges from the clavipectoral fascia, along with the lateral pectoral nerve, medial to the insertion of pectoralis minor on the coracoid process, a bony prominence that can be felt below the clavicle near the junction of its middle and outer thirds. The point, 2–3 cm medial to the coracoid process, represents the surface marking of the vascular hilum of the muscle. The vessels do not enter the muscle belly immediately but run on its deep surface in a downward and medial direction giving off its branches. The acromiothoracic artery gives off a superior (clavicular) branch to the clavicular segment of the muscle and a main pectoral branch, which then gives off an inferior thoracoacromial branch to the sternal segment and a lateral thoracic trunk to the external segment.

In approximately 50% of cases, the external segment of the muscle may be supplied exclusively by the lateral thoracic vessels that arise from the second part of the axillary artery and descend along the lateral border of the pectoralis minor. In one-third of cases, this external segment receives a dual supply from both the lateral thoracic and the thoracoacromial vessels. The sternocostal segment also receives a supply immediately from a perforating branch of the internal mammary artery, which may account for significant bleeding during the raising of the flap. The pectoralis major flap has a Type V vascular pedicle.

The major advantages of this flap are that it has a large skin territory (the whole of the skin overlying the muscle may be raised), it has a rich vascular supply and it can be transferred without prior delay. It has a large arc of rotation and can be transferred up to the upper aspect of the ear to the level of the zygomatic arch. It can be harvested in the supine position, and can be transferred either as a muscle-only, skin and muscle paddle, or as two epithelial surfaces for inner and outer lining with a de-epithelialized segment between them. Primary donor site closure is easily achieved. However, it is a large bulky muscle that is relatively immobile and, therefore, is suited best to providing well-vascularized tissue to fill large defects where mobility is not of paramount importance, as in the repair of fistulae. It violates the breast in the female and, in this situation, the latissimus dorsi flap provides an appropriate alternative.

TECHNIQUE

The whole of the skin overlying the pectoralis major muscle may be raised if required. However, this will leave a large defect that will require coverage with a skin graft and so the flap is usually designed to facilitate primary closure.

With the patient in the supine position, the surface markings of the acromiothoracic artery are outlined. A dotted line is marked from the acromium to the xiphoid process and a further dotted line is dropped to join this line in a perpendicular direction from the sternal notch. The point at which the line bisects the first line represents the location where the vascular pedicle meets the first line (**Figure 92.11**). The pedicle then runs in the direction of the first line from the acromium towards the xiphisternum. The clavipectoral fascia is then marked by a point two-thirds of the distance along the clavicle from the sternal

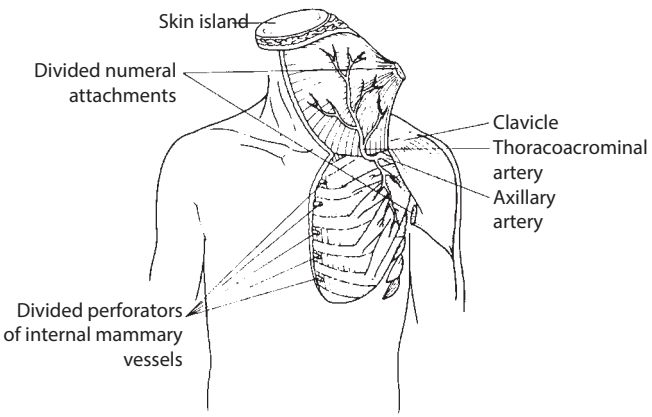

Figure 92.10 Blood supply to the pectoralis major myocutaneous flap.

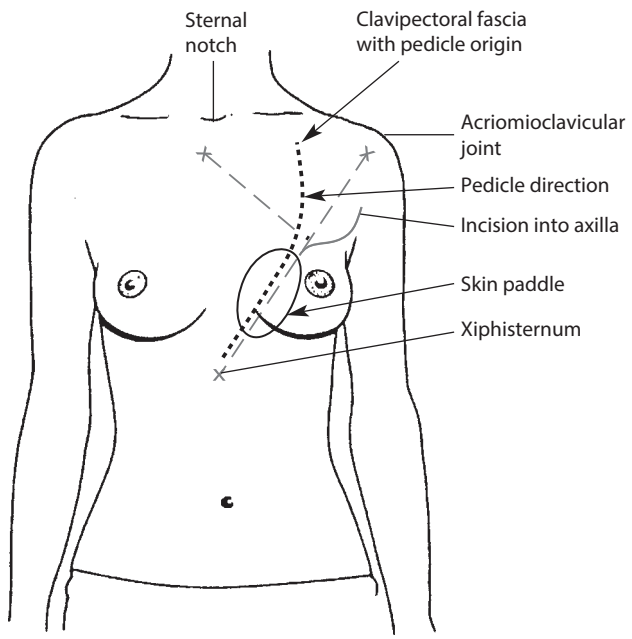

Figure 92.11 Landmarks for raising the pectoralis major myocutaneous flap.

notch to the coracoid process. The vascular pedicle runs in a curved direction downwards to meet the bisection point already described. A skin island of the appropriate size and shape may be drawn over the distal part of the artery, to facilitate a suitable arc of rotation. The borders of the skin paddle should lie between the lateral edge of the sternum medially and the nipple laterally. The incision for access should be extended into the axilla. The technique described by McGregor and McGregor[2] (i.e. designing the skin incision to allow a secondary deltopectoral flap from the same side) should be considered in both males and females. This technique allows for an easier wound closure and provides a salvage flap for neck resurfacing.

Unless the arc of rotation needs to be increased, it is advisable not to extend the lower part of the skin paddle beyond the inferior edge of the muscle. This part of the flap is random and, although the survival of this segment can be increased by taking part of the rectus sheath, this is not wholly reliable and should not be done unless absolutely necessary. Remember that the flap will retract by 10% in all directions when the skin is cut and this should be allowed for in planning, although some expansion will occur when the muscle is sewn in under tension.

The steps for elevation of the pectoralis major flap are as follows:

1. Start the dissection inferiorly.
2. Incise the skin down to the underlying muscle.
3. Define the inferior and lateral borders of the pectoralis major muscle.
4. Incise and mobilize the inferior attachments of the muscle to gain access to the subpectoral plane, which is relatively avascular.
5. Divide the inferior muscle attachments from the ribs or rectus sheath.
6. Mobilize in an upward direction.
7. At this point the pectoralis minor muscle will be visualized.
8. If the skin paddle is thick or excessively mobile, place sutures from the dermis of the skin island to the muscle surface to prevent shearing and flap loss.
9. Combine mobilization in an upward direction, first laterally and then medially.
10. Identify the lateral border of the external segment of the muscle.
11. Identify and ligate the major branch of the lateral thoracic artery to increase the arc of rotation.
12. Continue the dissection upwards.
13. Divide the sternal insertion of the muscle at the level of the anterior axillary line and remember to continue in a vertical direction.
14. Do not curve the scissors medially at this point or you may cut the pedicle – the ultimate disaster.
15. The muscle will now be rotated and the vascular pedicle will be clearly identified.

Once the origin of the sternal portion of the muscle has been divided, the flap may be easily elevated by blunt dissection in the subpectoral fascial space between pectoralis major and minor. The vascular pedicle is now clearly seen and the sternal edge of the muscle may be divided up to the level of the clavicle with the pedicle in clear view. Haemostasis is maintained throughout the elevation of the flap by carefully cauterizing the intercostal perforators, as well as the perforators supplying the medial portion of the muscle from the internal mammary vessels. If there is any lateral muscle mass attachment this is divided at this point, bearing in mind that the axillary vein is extremely close. The flap is now fully raised and mobile and if further mobility and arc of rotation are required, it may be islanded on the vessels by dividing the remaining muscular pedicle.

As a teaching aid, it is prudent to observe the neurovascular pedicle of the pectoralis minor muscle at this point, which is now visible and easily accessible. This muscle may be raised on its own as a free flap and used in facial reanimation techniques (see Chapter 95, Facial reanimation surgery).

Whilst the flap is being sewn in at the recipient site, the donor site can usually be closed. Haemostasis must be carefully achieved. Two large drains are inserted and the defect is closed, primarily using a two-layer closure. If closure is anticipated to be difficult, a one-layer blanket nylon or Ethilon stitch is an elegant technique of closing the wound as it takes up the tension gradually in the same way as a mastectomy wound is closed. Large defects may require a skin graft.

Modifications of the flap include harvesting of muscle alone when, for example, closing large lower neck wounds that require bulk with no skin paddle. A subsequent skin graft can be applied to the raw muscle surface. Access is achieved along the lateral border of the muscle and primary closure easily achieved. The incorporation of vascularized bone has been described where part of either the fifth rib or the sternum can be transferred with the flap to provide composite soft tissue and bony reconstruction. The vascular supply to these bony segments is at best precarious and in the majority of instances non-existent. Newer and more effective techniques for composite soft-tissue and bony reconstruction are available, obviating the need for the myo-osseous pectoralis major flap. Double skin paddles may be used with de-epithelialized islands in between them to provide oral lining and cutaneous cover but, again, in this situation, the muscle is very bulky and newer techniques such as double-paddled radial forearm flaps are probably better. Where the excessive bulk of the pectoralis major is a problem, harvesting over the thinner, parasternal area has been described (e.g. to tube the flap for reconstruction in the hypopharynx). Although this sounds attractive, practical experience has shown that it is virtually impossible to tube a pectoralis major myocutaneous flap. This should be considered as a salvage technique only, as better free tissue transfer techniques are available

When the above guidelines are followed, there are very few potential pitfalls with this flap. It is highly reliable and even when the skin paddle fails, the underlying muscle will usually survive and can be allowed to granulate and heal by secondary intention, or covered subsequently with a skin graft. It is always worth checking for congenital

absence of the pectoralis major, although it is extremely rare, with an incidence of 1 : 11 000. Congenital absence of the sternocostal head is part of Poland syndrome.

When a conventional flap is used, the skin paddle is designed medial to the nipple, at about the level of the sixth rib. In this area, the skin overlying the muscle is usually relatively thin in males. To achieve similar thickness in females, a design placing the skin island in the inframammary fold oriented transversely or slightly angled superiorly in its medial extent allows for the thinnest flaps. Where greater flap length is required, the flap design may be extended inferiorly beyond the lower border of the muscle. The extension should not extend beyond 3–4 cm and the rectus abdominus aponeurosis together with the rectus sheath should be raised with the flap. In this situation, the survival of the lower part of the flap is unpredictable. The breadth of the flap may be extended by including the nipple/areolar complex. The design of the incisions for this flap is particularly critical in females, where vertical scars result in significant secondary deformities of the breast. The surgeon considering this flap in females should consider the inframmary incision as the preferred approach.

Latissimus dorsi flaps

This flap represents the first myocutaneous flap described in the medical literature (by Tanzini). It was repopularized by Olivari in 1976[14] for the repair of local defects. Further work by Quillen et al. in 1978[15] described its use for head and neck reconstruction, and it remains a reliable and versatile fundamental component of the surgeon's repertoire.

The muscle is large and triangular in shape and arises from the sacrum and lumbar vertebrae, thoracolumbar fascia, the posterior iliac crest and the lower six thoracic vertebrae. In addition, some slips arise from the lower three ribs and the muscle converges to have a narrow insertion into the intertubercular groove of the humerus. Hence, it forms the posterior wall of the axilla. It is a type V muscle, which receives a significant but smaller blood supply from the perforating vessels through the lumbosacral fascia, and a pedicled flap can be based on this to repair defects in the buttock region.

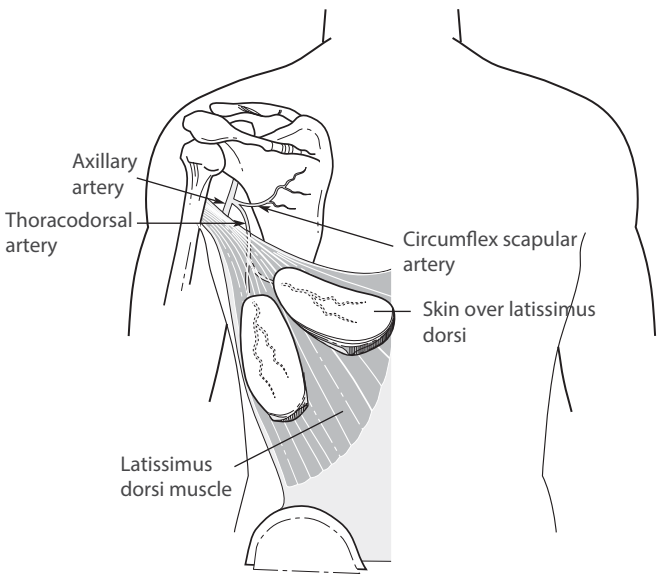

Figure 92.12 Blood supply to the latissimus dorsi flap. The thoracodorsal artery is a continuation of the subscapular artery, which comes directly off the axillary artery.

Its major vascular supply arises from the thoracodorsal vessels, which have their origin in the subscapular artery (**Figure 92.12**). This latter artery arises from the axillary artery, gives rise to the circumflex scapular artery about 4 cm from its origin (**Figures 92.13** and **92.14**) and then continues as a thoracodorsal artery to enter the latissimus dorsi about 10 cm from its humeral insertion. Just before its insertion, it gives off a branch that accompanies branches from the lateral thoracic artery (which also arises from the subscapular artery) and carries on to supply the serratus anterior. Within the latissimus dorsi muscle, the thoracodorsal vessels divide into superior and lateral branches that allow the muscle to be split into two. Either two flaps can then be taken or just one flap, thereby leaving some muscle behind.

Venous drainage is by the venae commitantes, which accompany the thoracodorsal artery and drain into the axillary vein. The nerve supply is via the thoracodorsal nerve, which is a branch of the posterior cord of the brachial plexus.

Large amounts of tissue are made available using this flap. Flaps measuring 10×8 cm are easily harvested and subsequent primary closure is easily achieved. Even larger amounts of tissue may be taken as a musculocutaneous flap measuring 40×20 cm but this requires skin grafting of the donor defect and may lead to problems with healing on the back.

A latissimus dorsi flap may not only be raised as a myocutaneous pedicled flap but also used for free tissue transfer. It is reliable, with a long pedicle of greater than 10 cm which can be further lengthened by dividing the circumflex scapular artery. The diameter of the subscapular artery at this point is at least 3 mm and the veins are of similar size.

By designing the flap low down on the back, the arc of rotation allows transfer into the head and neck region up to the zygomatic arch and flaps can be made to reach the top of the head (particularly if only muscle is used). The other advantages of this flap are that it does not violate the breast and because it is a large flat muscle, it is possible in extreme circumstances to tube it for total pharyngeal reconstruction. In addition, the subscapular artery offers a variety of flaps which may be used either singularly or in combination. Therefore, a scapular flap along with a latissimus dorsi flap and serratus anterior flap may all be raised on the same pedicle.

The advantages of the latissimus dorsi flap are:

- large amounts of tissue can be transferred
- pedicled or free tissue transfer
- it has a cosmetic advantage, especially for females
- it is versatile; may be tubed/multiple/osseous components
- when pedicled, it can reach the upper face and scalp.

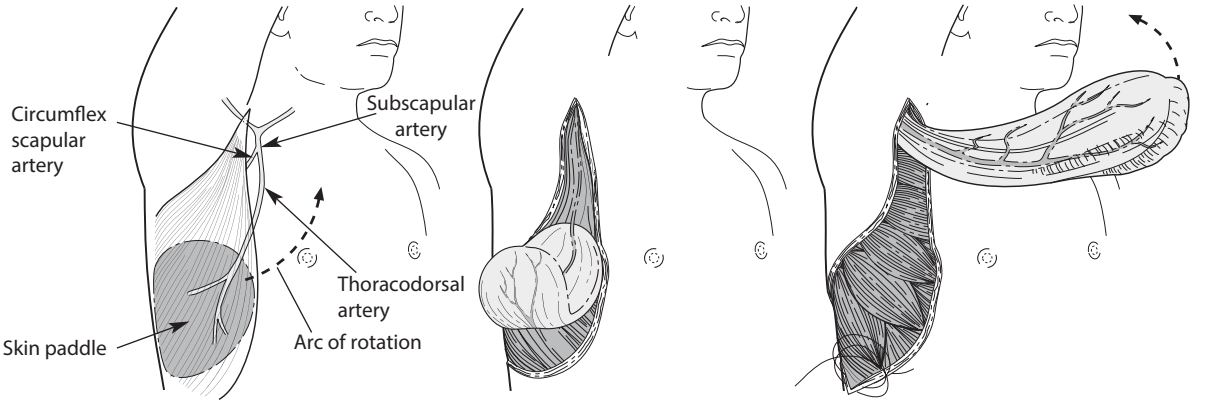

Figure 92.13 Technique of raising the latissimus dorsi flap. When designing for pedicled transfer, an oblique incision is used to allow maximal length to the flap. The dissection begins low down and then the pedicle is identified more proximally as the dissection approaches the axilla.

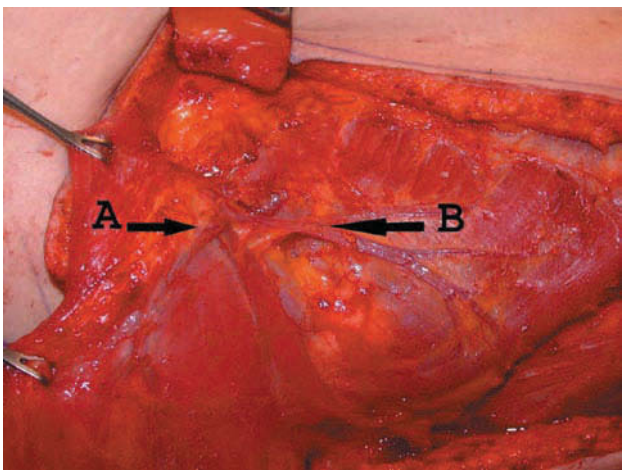

Figure 92.14 Lateral view latissimus dorsi pedicle. (a) Thoracodorsal branch to latissimus dorsi; **(b)** thoracodorsal branch to serratus anterior.

Despite these advantages, it still remains a musculocutaneous flap with thick skin and is therefore more bulky than, for example, a radial free forearm flap. Its use tends to be in resurfacing large defects of the external neck skin and for secondary repair of wound complications such as salivary fistula. It has an excellent application in reconstructing the total glossectomy defect as the volume of the flap makes it ideal for filling the mucosal defect and the dead space below the resection site. Serious donor site problems are rare but dehiscence and late wound seroma can be a problem. Congenital absence of the muscle should be checked for prior to surgery, and in athletes and those who do manual work the flap should be raised from the non-dominant side.

Raising the flap usually involves a variable amount of turning of the patient. Some authors advocate the lateral decubitis position, which often requires a repositioning manoeuvre following the ablative procedure. Most surgeons who are experienced with this flap will harvest it with the patient turned 15–30 degrees, which obviates the need for the repositioning manoeuvre and allows two team procedures.

The disadvantages of the latissimus dorsi flap are:

- it is very bulky
- there is occasional donor site dehiscence
- reduction in upper limb power
- it may require moving of the patient to harvest.

RAISING THE FLAP

Small flaps may be raised with the patient supine, but larger flaps require the patient in a rotated position with the arm freely draped so that it may be moved during the flap harvest.

Skin may be raised over the whole area of the muscle, although the vascular supply from the thoracodorsal artery decreases as one approaches the lumbosacral fascia. The posterior axillary fold is marked out and this represents the anterior edge of the muscle. The posterior iliac crest is also marked, together with the tip of the scapula. The skin flap is designed to the appropriate size and shape, with particular reference to the length of pedicle. If an arc of rotation is required to facilitate transfer to the head and neck via a pedicled myocutaneous flap, it will usually mean an oblique or vertical design; but if a free flap is required, the flap may be harvested in a horizontal direction, which gives a more acceptable scar in young women since it can be hidden behind the bra strap.

The steps for elevation of the latissimus dorsi are:

1. Outline the flap.
2. The initial incision exposes the anterior edge of the latissimus dorsi muscle.
3. Dissect round inferiorly, cutting through the muscle.
4. Identify the serratus anterior.
5. Do not go deep to serratus anterior here: this places the pedicle in jeopardy.
6. Recognize serratus anterior, as its fibres run at right angles to those of the latissimus dorsi.
7. Divide latissimus dorsi inferiorly.
8. The muscle flap may be extended beyond the skin island in a lateral to medial and superoinferior direction to

provide additional muscle to resurface external defects or provide additional volume to fill defects. Remember at this point that if one is low and on top of the latissimus dorsi, the pedicle is not in jeopardy.
9. Elevate the flap in the submuscular plane.
10. Identify the pedicle running down the muscle, usually in its central portion. The key to easy identification and protection of the pedicle to latissimus dorsi is to identify the branches to the serratus and follow them superiorly to the take-off from the thoracodorsal. Occassionally, patients will have a separate pedicle to serratus but this is very infrequent. Once the thoracodorsal pedicle is identified, divide the vessels to serratus anterior and continue dissecting superiorly.
11. Continue the dissection up towards the tip of the scapula.
12. The junction of the thoracodorsal vessels with the circumflex scapular vessels to form the subscapular artery can be clearly seen at the upper anterior end of the muscle in the axilla.
13. If a longer pedicle is required (as is usual), ligate the circumflex scapular vessels.
14. Follow the subscapular vessels into the axilla.

At this point, it is usual to island the flap if a free transfer is required. This also can provide a longer pedicle for the myocutaneous rotation flap. The surgeon may insert a pair of scissors under the latissimus dorsi tendon above the vessels and then cut the muscle to complete the islanding. When using the flap as a myocutaneous rotation flap, consideration should be given to not dividing the insertion of the muscle. When the muscle is left intact, the insertion prevents twisting of the vascular pedicle and reduces the risk of kinking and venous congestion. If an extended pedicle is required than the tendon must be divided to get additional length.

There are two steps in the delivery of the latissimus dorsi flap:

1. Ligate the circumflex scapular artery and vein.
2. Follow the subscapular vessels into the axilla.

If a pedicled transfer is to be completed, the flap must be tunnelled into the neck. There are essentially two options, sub- or suprapectoral, with the subpectoral route being the favoured approach. The border of the pectoralis major is identified and dissection deep to the muscle establishes the space between pectoralis major and pectoralis minor. A tunnel may be developed with blunt or sharp dissection, making sure that the pedicle to the pectoralis major is kept medially. The surgeon then develops the superior dissection, if it has not already been performed, by exposing the clavicle and the clavipectoral fascia. A tunnel is then developed by splitting the pectoralis major. The tunnel needs to be wide enough to allow the passage of the muscle without compression, usually the breadth of one's hand:

1. Use blunt finger dissection going on top of the pedicle.
2. Remember to go 'over pectoralis minor – under pectoralis major'.
3. Dissect from above through the clavipectoral fascia, dividing some of the lateral fibres of pectoralis major.
4. Open and widen the tunnel.
5. Deliver the flap without twisting or rotating the muscle.

The donor site is closed primarily in two layers using two large drains, one of which should be left for up to a week to avoid a seroma, which can occur following such a large dissection. This can be avoided by suturing the muscle remnants to the chest wall prior to closure. With a pedicled flap, the muscle should be denervated by dividing the nerve. If a free flap is being used, the thoracodorsal nerve may be preserved and used for reinnervation procedures such as anastomosis to a cross facial nerve graft for facial reanimation, or following total glossectomy where the maintenance of muscle bulk has been noted following anastomosis to the hypoglossal nerve.

Sternomastoid flaps

The sternocleidomastoid muscle, unlike the previously described muscles, does not have a localized vascular hilum. It is supplied segmentally by vessels that enter the muscle at intervals along its length. There are two principal vessels in its upper half, which consist of two branches of the occipital artery, and in its lower half, a branch from the superior thyroid artery. Further minor arterial branches enter in between. Its use has been described as: a myocutaneous flap raised as a composite skin muscle flap; a myocutaneous skin island flap taking a skin island based over the lower aspect of the muscle (**Figure 92.15**); or a composite muscle–bone flap used for mandibular reconstruction taking a segment of clavicle. Its routine use is not recommended as it has a number of distinct disadvantages:

- The upper sternomastoid composite skin muscle flap is poorly vascularized and not reliable.
- The blood supply to the skin paddle based over the lower third of the muscle is similarly unreliable.
- The upper and lower ends of the muscle are areas of oncological significance.
- The inclusion of clavicle for mandibular reconstruction is usually no longer required as superior reconstructive options are available.

The sternomastoid flap is therefore rarely used but it may still have a role to play in two situations: first, it can be particularly useful as a muscle-only flap pedicled superiorly to fill small defects in the pharynx and oral cavity; and second, when split along its length and rotated anteriorly, it may be used to cover vessels in the compromised neck.

Trapezius flaps

Three basic myocutaneous flaps have been described that make use of trapezius: the upper trapezius, the lateral trapezius and the lower trapezius flaps.[16] These may be pedicled into the head and neck area and, in addition, descriptions of the upper and lateral trapezius flaps to include transfer

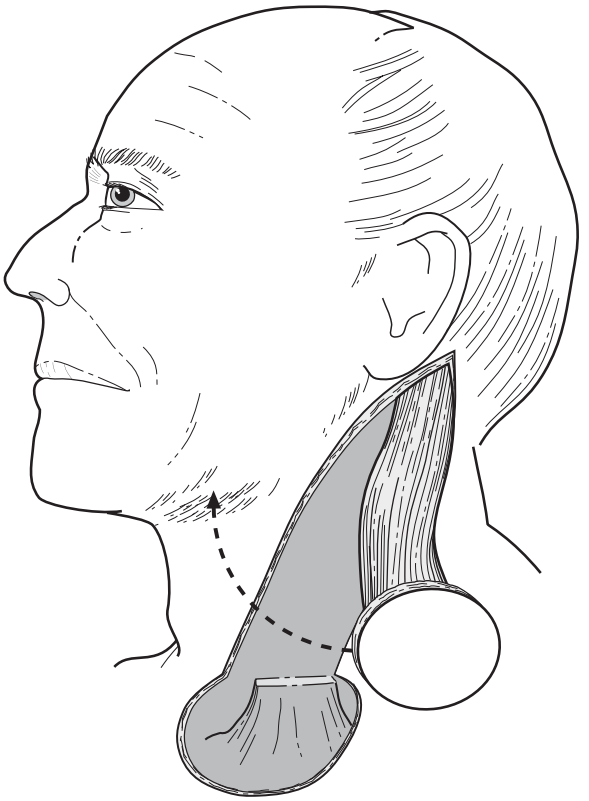

Figure 92.15 Sternomastoid flap.

of the spine of the scapula have been described for mandibular reconstruction. The vascular supply of these flaps is complex and varied depending on the design.

The superiorly based trapezius flap incorporates the upper third of the trapezius muscle and the overlying skin. The flap is supplied predominantly by the occipital artery and its venae commitantes. This flap has a limited used but can be applied for defects of the temporal bone, lateral face or upper neck. The flap is harvested by designing a skin island over the pars descendens of the trapezius muscle with dissection carried out in a retrograde direction along the deep surface of the muscle.

The pars horizontalis (middle) and a pars ascendens (lower) of the trapezius muscle form the basis of the lateral and lower trapezius flaps (**Figure 92.16**). The middle parts of the muscle are supplied mainly by the superficial cervical artery (superficial branch of the transverse cervical artery) and the lower part is supplied by the dorsal scapular artery (deep branch of the transverse scapular artery) and segmental intercostals perforators. The origins of the arteries supplying the trapezius muscle are highly variable and the aforementioned vessels may arise from different trunks.

An anatomic study[17] published in 2004 has demonstrated that the superficial cervical artery always runs lateral to the levator scapulae and rhomboid muscles, dividing into a short superior branch and long inferior branch that courses inferiorly with the accessory nerve to the level of the scapular spine. The dorsal scapular artery – the dominant supply to the lower third of the muscle – runs deep to the levator scapulae and minor rhomboid muscles.

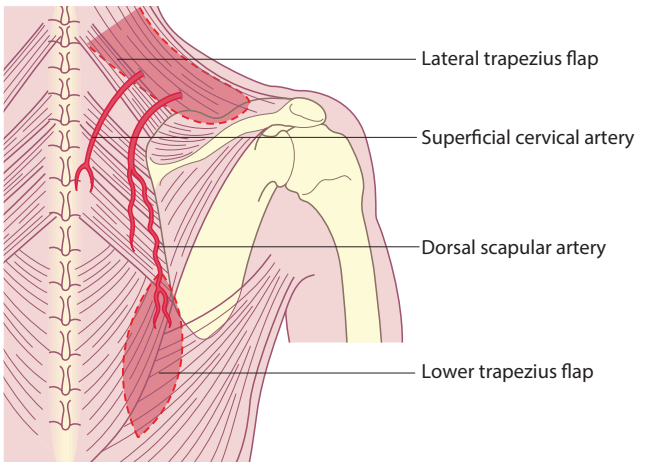

Figure 92.16 The trapezius group of flaps.

The flap with the most utility for head and neck reconstruction is the pedicled lower trapezius myocutaneous flap. This version of the flap has an arc of rotation appropriate for resurfacing of the neck and face and has great utility as a salvage option when a free tissue transfer has failed or there are no recipient vessels available for anastomosis of a free tissue transfer. The patient is positioned in the lateral decubitus position with the arm draped freely for repositioning of the scapula during dissection. The muscle margins, the medial border of the scapula and the thoracic spines down to the 12th vertebra are marked. The skin island is usually designed with the majority of the flap overlying the lower trapezius. Dissection begins medially, identifying the superior and lateral borders of the latissimus dorsi muscle and the lateral border of the trapezius. Dissection continues under the trapezius muscle where the dorsal scapular artery is identified. Retrograde dissection continues, following the vascular pedicle of the flap. The descending branch of the dorsal scapular artery (running deep to the rhomboids) must be divided to allow rotation and complete elevation of the flap. Dissection can be carried up to the levator scapulae with occasional division of the minor rhomboids to improve the arc of rotation. The flap can then be tunnelled subcutaneously into the neck.

Although these flaps are reasonably reliable and may play a role, particularly in the repair of the posterior aspect of the head and neck, such areas are easily reached with a pedicled latissimus dorsi flap. The patient positioning issues and anatomic variability related to the trapezius flap mean that it has a limited role to play in current head and neck reconstructive practice. Its role is principally to salvage (e.g. as a lifeboat when other flaps have been exhausted).

Platysma flaps

The platysma flap was first described in 1978. It is really one half of the myocutaneous apron flap and the skin transferred can either be at the level of the hyoid or in the supraclavicular region, after which the donor site is closed primarily. The blood supply to the upper part of the flap

comes from the submental branch of the facial artery and to the lower part from a branch of the transverse cervical artery. Although initially attractive as a simple way of providing a method of intraoral reconstruction, this flap has a number of distinct disadvantages and is rarely used today:

- Blood supply can be unreliable.
- There may have been previous surgery that has violated the neck and therefore precludes its use.
- When based on the submental branch of the facial artery, this requires preservation of muscularity in an area of oncological significance that may have to be addressed in the resection.
- By and large, the neck should be avoided as a source of reconstruction for the oral cavity.
- Removal of the platysma interferes with the blood supply to the overlying skin, which can have disastrous results.

CONCLUSION

While there has been a dramatic increase in the use of free tissue transfer in head and neck reconstruction, pedicled local or regional flaps have a major role to play in head and neck reconstruction. A clear understanding of the principles of use of local flaps and a comprehensive understanding of the anatomy of these flaps provides the head and neck surgeon with a plethora of local and regional options for primary and secondary reconstruction.

BEST CLINICAL PRACTICE

✓ With the axial muscular flaps, although the blood supply to the muscle is axial, the blood supply of the skin upon the muscle is random.
✓ There is a minimum size of skin paddle that should be taken to ensure that one incorporates sufficient perforators to supply the skin flap. For pectoralis major and latissimus dorsi flaps, this usually means a skin paddle measuring 5×3 cm (the size of the palm of an adult's hand).
✓ Smaller skin paddles may not survive.

FUTURE RESEARCH

➤ Numerous techniques have described using local and myocutaneous flaps in head and neck surgery. Unfortunately, very little data exists evaluating the outcomes in terms of the functional and aesthetic results.
➤ The field of local and myocutaneous flaps is additionally challenged by the advent of free tissue transfer that has dramatically reduced the need for complex local reconstructions except in reconstruction of the external skin.
➤ Future research in all areas of head and neck reconstruction should be focused on functional outcomes: speech, swallowing, aesthetics and patient quality of life.

KEY POINTS

- Pedicled flaps are usually straightforward to both use and harvest.
- Pedicled flaps are generally reliable, but may be bulky and poorly pliable.
- Pedicled flaps can be useful for salvage, particularly in the presence of infection.
- Pedicled flaps may be associated with significant donor site problems.
- Pedicled flaps should be in the surgical repertoire of every head and neck surgeon.

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CHAPTER 93

RECONSTRUCTIVE MICROSURGERY IN HEAD AND NECK SURGERY

John C. Watkinson and Ralph W. Gilbert

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SEARCH STRATEGY

Data in this chapter may be updated by a Medline search using the keywords: angiosome, perforator flap, free tissue transfer, fluid management, prophylaxis, deep vein thrombosis (DVT), Doppler, medicinal leech, free flap salvage, fibrinolysis, forearm flap, lateral arm flap, scapular flap, facial recontouring, scalp reconstruction, rectus abdominus, deep circumflex iliac artery (DCIA), anterolateral thigh flap, fibular flap, mandibular reconstruction, pharyngeal reconstruction, jejunal transfer and gastro-omental flap.

INTRODUCTION

Over the past 30 years, the introduction of reconstructive techniques incorporating microvascular free tissue transfer has transformed the quality of life of patients undergoing head and neck surgery. The microsurgeon's ability to transfer autologous tissues comprised of bone, functioning muscle, skin or composites has dramatically improved functional outcomes for all head and neck reconstructive procedures, whether oncologic, congenital or traumatic.

The revolution in the understanding of the blood supply to the various anatomic regions of the body[1,2] has dramatically increased the number and variety of reconstructive options. The wide variety of flaps and the breadth of anatomic knowledge required to offer patients the full panel of flaps available has demanded that most microvascular surgeons acquire specialized training. This evolution has also led to the development of specialized units offering the highest quality reconstruction and outcomes based on the effect of high surgical volumes and the inherent development of advanced technical expertise that comes with extensive surgical experience.

CLASSIFICATION OF FREE FLAPS

A variety of classification systems has been advocated for the description of the various types of free flaps available for reconstruction. A simple classification would divide flaps into cutaneous flaps, including fascia, subcutaneous fat and skin; myocutaneous flaps, including muscle with cutaneous elements; osseocutaneous flaps, including bone and cutaneous elements; and myo-osseous flaps combining muscle and bone.

Most recently a great deal of interest and terminology has evolved around the concept of perforator flaps (**Figure 93.1**).[3] A perforator flap consists of skin and/or subcutaneous tissues supplied by a perforating vessel that passes through or between the deep tissues, usually muscle. A muscle perforator is a vessel that traverses through muscle to supply the overlying skin. A septal perforator is a vessel passing only through an intermuscular septum to supply the overlying skin. A flap vascularized by a muscle perforator is called a muscle perforator flap and a flap vascularized by a septal perforating vessel is called a septal perforator flap. Based on this nomenclature, flaps may be described based on the anatomy of their supplying

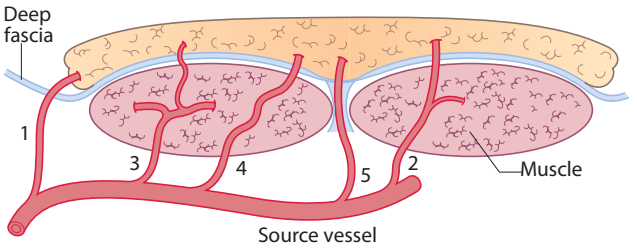

Figure 93.1 Schematic drawing of the different types of direct and indirect perforator vessels with regard to their surgical importance. 1, Direct perforators perforate the deep fascia only; 2, indirect muscle perforators predominantly supply the subcutaneous tissues; 3, indirect muscle perforators predominantly supply the muscle but have secondary branches to the subcutaneous tissues; 4, indirect perimysial perforators travel within the perimyssium between muscle fibres before piercing the deep fascia; 5, indirect septal perforators travel through the intermuscular septum before piercing the deep fascia. Redrawn from Ref. 3, with permission.

vessels. For example, the perforator based skin flap arising on the deep inferior epigastric artery that traverses the rectus abdominus muscle is called the deep inferior epigastric perforator flap and is a muscle perforator flap.

GENERAL CONSIDERATIONS IN FREE TISSUE TRANSFER

Peri-operative management

Considerable literature exists regarding the peri-operative management of patients undergoing free tissue transfers. In general, it is probably fair to state that there exists very little level I evidence regarding best practice. Numerous authors have advocated and continue to advocate for pre- or peri-operative use of volume expansion, particularly with synthetic plasma expanders.[4, 5] Many authors have advocated for higher than normal volume replacement during surgery in order to reduce the risk of arterial or venous occlusion. The evidence would suggest that none of these measures affect flap outcome. Paradoxically, some evidence suggests that excessive volume replacement results in higher rates of flap loss because of the resultant peri-operative complications of congestive heart failure and its sequelae.

The surgeon engaged in free tissue transfer must anticipate a long operative procedure and the following issues must be addressed. The patient must be protected from pressure sores, as procedures in excess of 8 hours often result in pressure sores on the sacrum, heels and back. Long periods of immobility require the use of deep vein thrombosis prophylaxis. Depending on jurisdiction and local practice, this includes heparin prophylaxis and intra-operative and peri-operative use of compression stockings.[6, 7]

Post-operative management

Patients undergoing free tissue transfer are best managed in monitored units where appropriate flap checks and appropriate invasive and non-invasive monitoring is available. In many jurisdictions this is provided in an intensive care facility or its equivalent. In centres with large volumes of free tissue transfers, specialized peri-operative units have been developed staffed with nurses specially trained in the management of free tissue transfers. Monitoring techniques vary from simple observation to implantable flow probes. A number of devices have been developed to detect venous or arterial occlusion. These techniques include percutaneous Doppler of donor vessels, cutaneous laser-Doppler flow probes and implantable flow probes.[8, 9] Little evidence suggests that any modality other than specialized nursing care and frequent observation represents best practice, with most major centres using percutaneous flow probes and specialized nursing units.[10, 11]

Recipient vessels

The head and neck represent a rich supply of vessels for vascular anastomosis. In the era of radical neck dissection, venous recipient vessels were often a problem as most ablative surgeons sacrificed the jugular vein. In the past 30 years, with the move to more selective neck dissections except in advanced disease, venous recipient vessels have not been a problem. Most experienced surgeons rely heavily on the facial artery, superior thyroid artery and transverse cervical artery for recipient arterial supply. These vessels often have a long mobile segment and are ideally positioned for most head and neck defects. Most microvascular surgeons advocate end-to-side venous anastomosis, and the internal jugular vein is often used. Secondary options include the external jugular vein, or the group of veins associated with the transverse cervical artery. The key to optimal vessel selection is careful peri-operative planning and communication between the reconstructive and ablative team with regard to vessel options and preservation during ablative procedures. New technologies are available for vascular anastomosis, with many centres advocating the use of mechanical anastomotic devices to expedite venous repair and reduce the rates of peri-operative occlusion.[12, 13]

Management of flap failure

The use of a free flap for head and neck reconstruction represents a major investment both for the patient and the reconstructive team. In the majority of head and neck procedures, flap failure represents a major peri-operative complication and a potential catastrophe. The majority of flap failures require major revision procedures and can result in significant prolongation of hospital stays and a delay in the delivery of post-operative radiotherapy or chemoradiotherapy. The functional and esthetic sequelae of flap loss can be devastating for oncologic patients.

The rationale for intensive peri-operative observation is to detect venous or arterial occlusion early with an emergent return to the operative theatre to attempt to salvage the flap. Most series report salvage rates between 50% and 80% dependant on the timeliness of detection of venous or arterial occlusion and the speed with which

the problem can be corrected.[14] The majority of occlusions are venous based largely on low flow and likely the greater technical difficulty in suturing a venous anastomosis. Two adjunctive techniques are widely used for venous occlusion. Many authors advocate the use of localized perfusion of the occluded flap with fibrinolytic agents.[15, 16] These agents, when perfused locally (but not systemically), seem to improve the rates of flap salvage. The other technique that is used widely for venous failure is the application of medicinal leeches. A detailed description of leech use is beyond the scope of this text, but they can be extremely effective at salvaging venous occlusions.[17]

FREE FLAPS IN HEAD AND NECK RECONSTRUCTION

The forearm flaps

The free forearm flap was first described for head and neck reconstruction by Yang[18] in 1983 when he used this flap to reconstruct a neck defect secondary to a burn scar contracture. The forearm flap was popularized for head and neck reconstruction by Soutar et al.[19] in 1983. Soutar described the first large series of forearm flaps for oral reconstruction, as well as the osseocutaneous forearm flap that incorporated the radius for mandibular reconstruction.[20] Numerous authors have published series of forearm flaps demonstrating its utility and versatility in head and neck reconstruction.

ANATOMY

The cutaneous forearm flap is based on the radial artery with venous drainage provided by the venae comitantes or branches extending from the skin to the cephalic vein of the forearm (**Figure 93.2**). The artery and venae have a remarkably consistent anatomy with rare anatomic variations. The vessel generally lies between the tendons of the brachioradialis and the flexor carpi radialis in the distal third of the arm and lies deep to the brachioradialis in the proximal forearm. The vascular supply to the skin is provided by perforating vessels that extend vertically through the overlying fascia to supply the subcutaneous fat and skin. The osseocutaneous version of the flap requires the incorporation of perforating vessels that cross over the velar and lateral surface of the radius to supply the periostemon of the distal radius. The flap can incorporate a sensory nerve – the lateral ante brachial cutaneous nerve of the forearm, which can provide a sensate flap for oral reconstruction.

The skin island can be as large as the entire velar surface of the arm. The bone available is from the pronator teres insertion to the distal radius with a maximum length of 10–12 cm available.

ADVANTAGES

The forearm flap has a number of unique advantages for head and neck reconstruction. Its surgical anatomy is remarkably consistent, making it a relatively easy flap for surgeons to learn and harvest reliably. The skin on the distal third of the arm is extremely thin, making it an ideal flap for interiorly reconstruction of the lateral tongue and floor of mouth. The flap can be harvested as a sensate flap, providing the most robust sensation available of all the cutaneous flaps available for head and neck reconstruction.[22] Because of the positioning of the arm during surgery the flap can be harvested simultaneously with an ablative head and neck procedure.

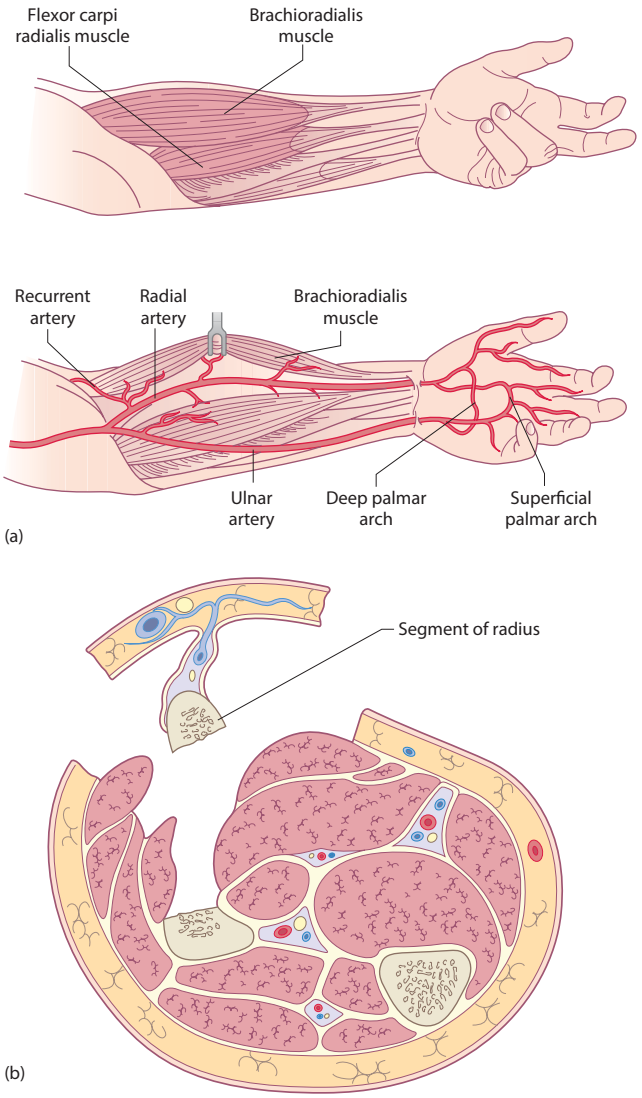

Figure 93.2 Detailed anatomy of the forearm flap: (a) muscular and vascular anatomy; **(b)** coronal section of the forearm illustrating the osteocutaneous version of the forearm flap, note the perforators extending from the radial artery to the overlying skin as well as the lateral and descending perforators to the radius. Redrawn from Ref. 21, with permission.

DISADVANTAGES

The forearm flap has few disadvantages. In terms of match to recipient defects, its only liability is the volume of tissue for some defects that incorporate large mucosal or cutaneous defects with a considerable amount of dead space.

The skin colour match to external skin is probably the poorest of the cutaneous flaps, except in patients of South Asian or African American origin, for whom the flap can have an excellent colour match. The donor site is not popular with patients as it usually requires a skin graft, leaving a relatively unsightly scar on the velar forearm. Bardsley et al. have described a so-called hatchet flap variation utilizing a volar ulnar artery based flap for primary closure of the forearm defect (**Figure 93.3**).[23] Other potential problems include wrist stiffness, cold sensitivity and, on occasion, tendon exposure, which often require long periods of wrist splinting to ultimately achieve skin closure.

TECHNICAL NUANCES

This flap is usually harvested under tourniquet control offering a blood free dissection. It is critical to be certain prior to harvest and tourniquet inflation that the patient has a patent lunar artery. In most patients the lunar artery is the dominant blood supply to the deep palmer arch that supplies the hand and digits. A simple Allen's test to evaluate collateral flow through the lunar artery is a mandatory pre-surgical procedure. During the harvest it is important to avoid injury to the cutaneous branch of the radial nerve. To avoid problems with tendon exposure following harvest, the paratenon overlying the flexor carpi radialis must be preserved to well-vascularized surface for a skin graft. Most surgeons use a relatively thick split thickness skin graft for the donor site. Some series have reported success with the use of full thickness grafts. In terms of the bone harvest in the osseocutaneous version of the flap, the major complication associated with this flap is fracture of the distal radius at the site of the bone harvest. The distal radius proximal to the radial styloid is relatively narrow and too vigorous a bone harvest can result in radial fracture. Most authors advocate taking no more than one-third of the width of the radius, and also suggest curving the osteotomy, avoiding perpendicular bone cuts, which can produce stress risers and potential fracture sites.[24] Some authors advocate prophylactic plating of the distal radius if a bone harvest is performed.[25] Most experienced microvascular surgeons would avoid this osseocutaneous flap in elderly osteoporotic females.

APPLICATIONS

Oral cavity and oropharynx

The forearm flap was popularized by Soutar for oral reconstruction and is the most important application for this flap in head and neck reconstruction. The function of a reconstruction of the oral tongue is to retain the mobility of the tongue remnant. One can easily appreciate that the forearm is ideally suited to the task (**Figure 93.4**). This flap's thin subcutaneous layer, pliability and potential sensation makes it unique among the variety of cutaneous flaps available for oral reconstruction. In defects including a segmental mandibular defect, authors have advocated the use of the osseocutaneous forearm flap. The radius is a less than ideal reconstruction for even short mandibular defects. It has a short vertical height, making secondary prosthetic reconstruction of the dental arch difficult or impossible, particularly if osseointegrated implants are indicated. In addition, the short length of available bone is problematic for extended defects. The radius is not easily osteotomized for defects including the symphysis or angle. Its only application in mandibular reconstruction is likely as a secondary option when the other bone flaps are not available or for short defects of the symphysis or body of the mandible. The osseocutaneous flap has been used for central maxillary defects, where a soft pliable cutaneous flap containing bone, associated with a long vascular pedicle, represents an ideal reconstruction (**Figure 93.5**).

The forearm is likely the best flap available for buccal mucosal reconstruction as it is the only cutaneous flap with the appropriate thickness for buccal defects.

This flap has been widely used for palate reconstruction, particularly small defects of the central palate and alveolus. Its unique strengths in this application are the thinness of the flap and its long vascular pedicle, which will readily reach neck recipient vessels.

Many reconstructive surgeons use this flap for defects of the oropharynx, particularly the tonsil–tongue base soft palate defect where the flexibility of the flap allows it to contour into these complex three-dimensional defects and provides excellent functional reconstruction of the soft palate.

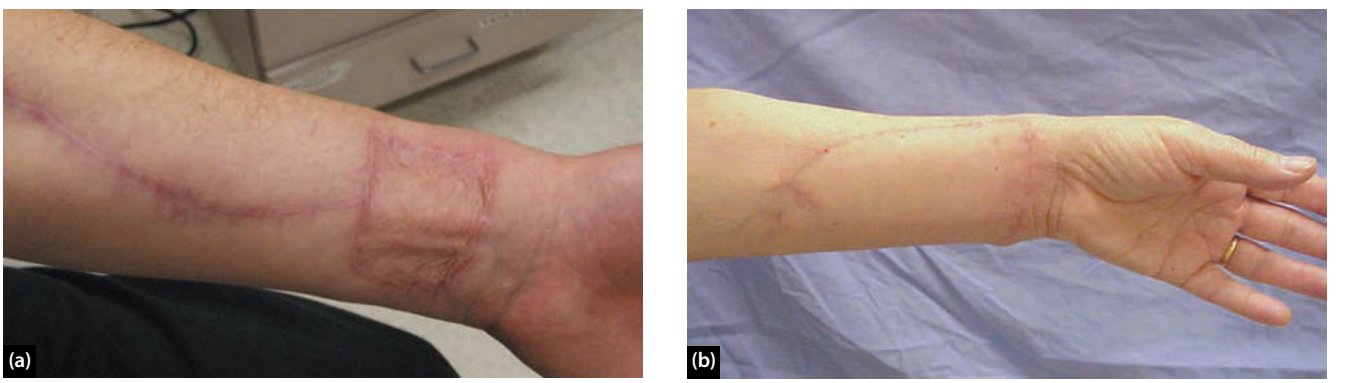

Figure 93.3 **(a)** Skin grafted donor site; **(b)** primary closure with hatchet flap.

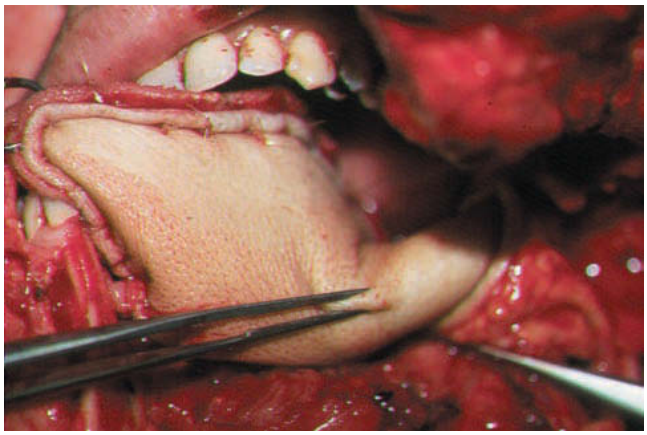

Figure 93.4 Oral tongue reconstruction with forearm flap.

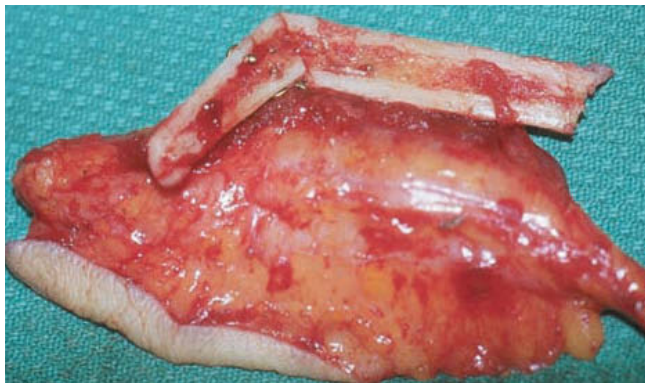

Figure 93.5 Osseocutaneous radius for midface reconstruction.

External skin

The forearm flap has been widely used for cutaneous defects of the head and neck. Because of the limited amount of skin available the applications for external defects are limited to small defects where the unique features of the flap are an advantage. One of the disadvantages of this flap in Caucasians is a relatively poor colour match to facial skin.[26]

The forearm flap's greatest applications in external skin reconstructions are the total upper or lower lip defect and total nasal reconstruction. In total lip reconstruction the ability to replace the entire aesthetic unit of the upper or lower lip along with a tendon sling (incorporating the palmaris longus or flexor carpi radialis tendon with the flap) makes this an excellent functional reconstruction for this formidable defect.[27] In total nasal reconstruction, a number of authors have described the use of this flap to create the lining and infrastructure for the nose, using a multistage procedure incorporating a forehead flap for external cover.

The lateral arm flap

The lateral arm flap described by Song et al.[28] in 1982 has been widely used in head and neck reconstruction. This flap has application in oral cavity reconstruction and in reconstruction of soft tissue and cutaneous defects of the face and neck. This flap has a relatively large cutaneous flap available up to 14 × 20 cm; however, donor sites wider than 6 cm cannot be closed primarily.

ANATOMY

This flap's blood supply is based on the radial collateral artery of the arm (**Figure 93.6**). The radial collateral artery arises from the deep brachial artery and runs with the radial nerve on the lateral aspect of the upper arm. Once the radial collateral appears on the anterolateral aspect of the trapezius it divides into a posterior and anterior branch. The anterior branch continues inferiorly to accompany the radial nerve deeply between brachialis and brachioradialis. The posterior branch enters the lateral intermuscular septum between brachialis and triceps and then runs toward the lateral epicondyle. In its course along the lower lateral arm the posterior branch gives off a number of fasciocutaneous perforators to supply the skin in this area. The skin of the lateral arm flap is innervated via the lower lateral cutaneous nerve of the arm a branch of the radial nerve. The innervation provided is relatively dense but not as sensate as the forearm flap.

ADVANTAGES

The major advantage of the lateral arm flap is its location on the arm. The donor site for this flap is relatively inconspicuous and can be closed primarily in most patients. The colour match to facial skin is excellent, even in Caucasians. The flap can be harvested as a sensate flap and does provide functional sensation.

DISADVANTAGES

The major disadvantages of the lateral arm flap relate to the available width of the skin flap and the pedicle size. Extremely wide flaps will require a skin graft for closure. The fat in the lateral arm may provide too much volume for oral reconstruction in obese patients. The pedicle associated is of small calibre with a maximum diameter of 1.5 mm with potential very small venae comitantes. Microsurgical anastomosis is therefore technically difficult and less reliable than other flaps. The vascular pedicle is short, 4–8 cm, making this flap less than ideal when recipient vessels are at a distance from the defect site.

TECHNICAL NUANCES

The flap design is critical to ensure that the posterior branch of the radial collateral artery is included in the flap. The axis of the flap and area to be harvested are planned by drawing a line from the deltoid insertion to the lateral epicondyle. Dissection begins on the posterior aspect of the flap with harvest of the deep fascia overlying the trapezius. Dissection continues superiorly until the lateral intermuscular septum is encountered. The posterior branch is visualized and then dissection begins on the anterior aspect of the flap again in the subfascial plane until the intermuscular septum is isolated on both sides. The flap is then dissected in a retrograde fashion with great care taken to avoid injury to the radial nerve.

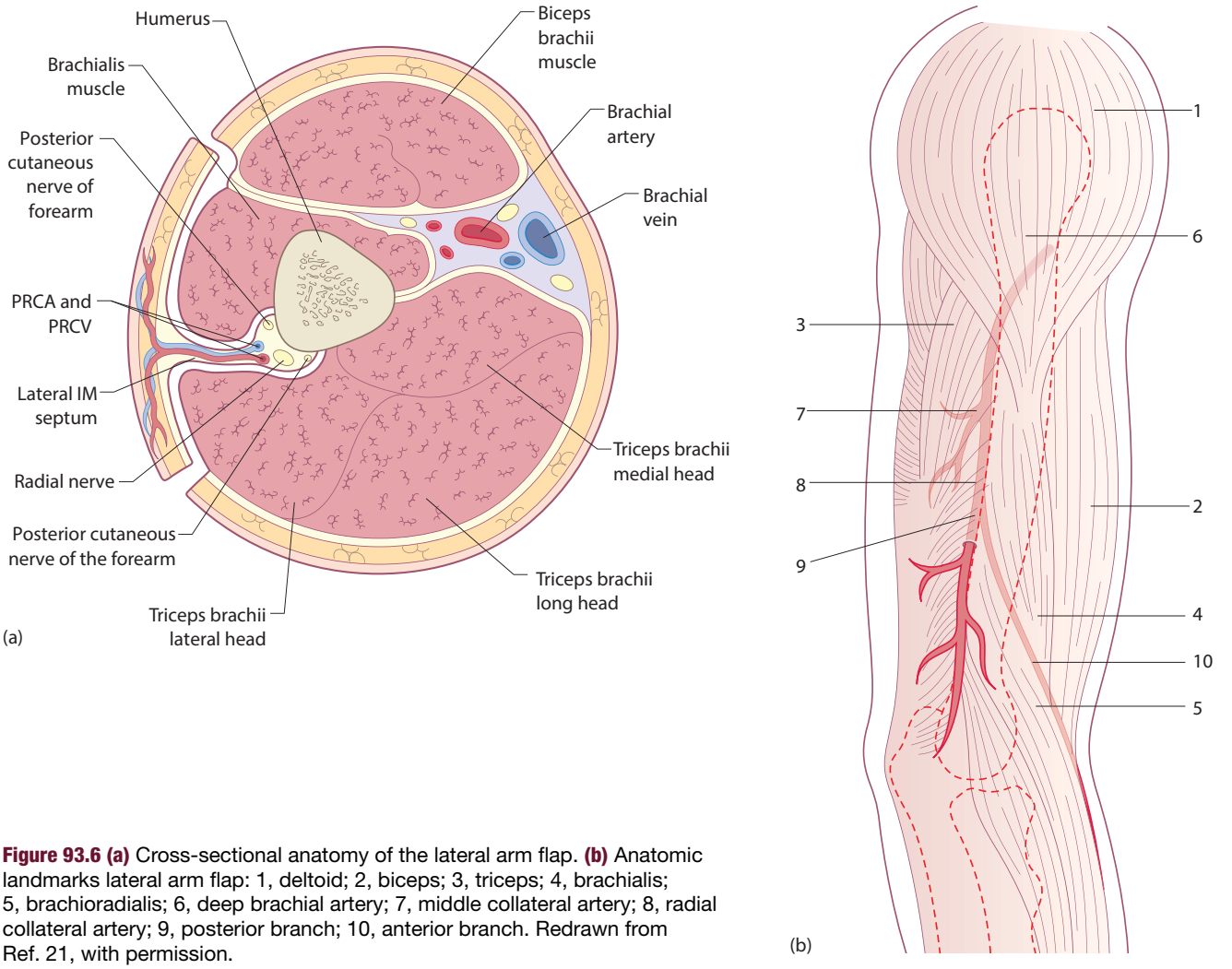

Figure 93.6 (a) Cross-sectional anatomy of the lateral arm flap. **(b)** Anatomic landmarks lateral arm flap: 1, deltoid; 2, biceps; 3, triceps; 4, brachialis; 5, brachioradialis; 6, deep brachial artery; 7, middle collateral artery; 8, radial collateral artery; 9, posterior branch; 10, anterior branch. Redrawn from Ref. 21, with permission.

CLINICAL APPLICATIONS

The major disadvantage of this flap is its pedicle length. It should not be considered when recipient vessels are at a distance from the defect site. The major applications for this flap are in reconstruction of the floor of mouth and lateral tongue. The excellent colour match to the lateral aspect of the face and neck make it ideal for recontouring radical parotidectomy defects or replacements for narrow defects of the lateral face or neck.[29]

SCAPULAR SYSTEM OF FLAPS INCLUDING THE LATISSIMUS DORSI FLAP

Cutaneous or osseocutaneous scapular or parascapular flap

The scapular system of flaps were popularized for head and neck reconstruction by Swartz et al.[30] and dos Santos.[31] A number of head and neck surgeons have described their experience with this flap in complex oromandibular reconstruction.[32]

The scapular system of flaps is unique in the area of head and neck reconstruction as no single area provides such a variety of options for reconstructive tissues. Flaps harvested from this group of flaps can provide skin, skin and muscle, skin and bone or skin, muscle and bone with two or three muscle flaps available based on a single vascular pedicle.

ANATOMY

In order to take full advantage of this group of flaps a detailed understanding of the vascular anatomy of this area is critical (**Figure 93.7**). The axillary artery gives rise to the subscapular artery, which descends in the posterior axilla to give rise to the circumflex scapular artery and the thoracodorsal artery. The circumflex scapular artery provides nutrient and periosteal supply to the lateral border of the scapula, then divides into two perforating branches that supply the skin overlying the scapula. The circumflex scapular artery lies in the space bordered inferiorly by the teres major muscle, superiorly by the teres minor muscle and laterally by the long head of the triceps. Once through this space the artery divides into the two aforementioned branches, giving rise to a parascapular perforator and a

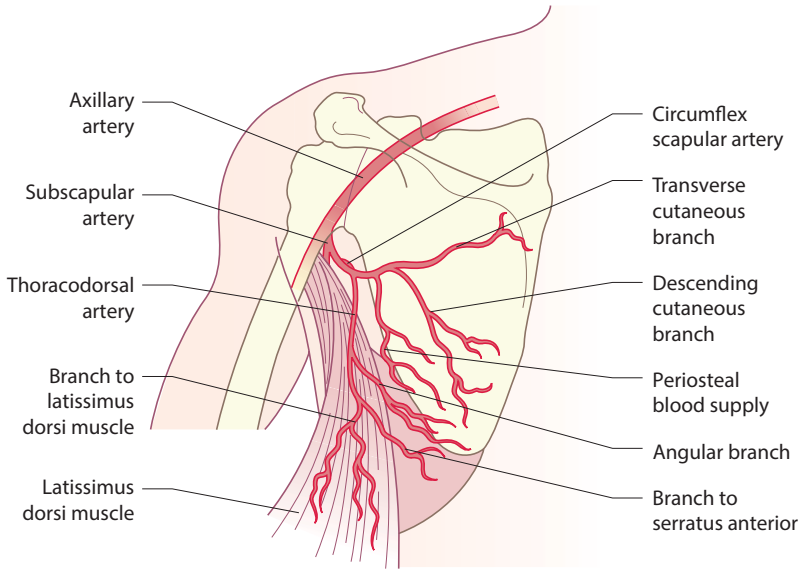

Figure 93.7 Anatomy of the scapular system of flaps. Redrawn from Ref. 21, with permission.

transverse scapular perforator. The thoracodorsal artery descends inferiorly, providing branches to the serratus anterior and the latissimus dorsi, as well as providing the angular artery, a branch that supplies the distal one-third of the scapula and its overlying musculature. The venous drainage is via paired venae comitantes, which usually join the axillary vein close to the origin of the subscapular artery. It can easily be appreciated from this vast array of vessels that any combination of flaps may be harvested depending on the requirements for the reconstructive defect. The cutaneous flaps available include a transverse scapular flap, a parascapular flap and a thoracodorsal artery perforator flap. The myocutaneous flaps available include the latissimus dorsi flap; the myogenous flaps available include serratus anterior, the latissimus dorsi and the teres major muscles. The osseous flaps include the scapular bone flap based on the nutrient vessels from the circumflex scapular artery or the scapular tip via the angular artery.

ADVANTAGES

The scapular systems of flaps have some particular advantages. The available skin, either via the parascapular or scapular perforators, can be as large as 18 × 10–12 cm with primary closure of the donor site. The latissimus dorsi perforator flap or the latissimus dorsi myocutaneous flap can provide even larger skin islands with primary closure of the donor defect. In composite reconstructions (bone and skin) the skin island may be rotated or positioned relatively independently of the bone flap, allowing considerable flexibility in positioning of the skin island relative to the bone segment. The vascular anatomy other than the blood supply to the tip of the scapula is remarkably consistent, and dissection based on anatomic landmarks makes the flap harvest relatively simple. The donor site when designed along the posterior axillary line is relatively well hidden. The skin colour of the scapular region generally is a good colour match to the face and neck, even in Caucasian patients. The donor site has very limited morbidity. However, when scapular bone is harvested most patients have some restriction of shoulder motion and require aggressive shoulder rehabilitation. It is the experience of a number of authors that this flap is extremely well tolerated in the elderly and vessels to the scapular system of flaps seem to be relatively spared in patients with extremity peripheral vascular disease, making it an excellent option in this group of patients.

DISADVANTAGES

This flap, while offering a plethora of reconstructive options, does have some disadvantages. In the original description of the harvesting of this flap the patient is positioned in the lateral decubitus position. For most ablative oncologic procedures, that would mean that the patient required repositioning for flap harvest and then a return to the original position for flap inset. Most experienced surgeons position the patient in the supine position with the body rotated 15–20 degrees. This positioning allows the ablative procedure and flap harvest without repositioning. Two teams or simultaneous harvest is next to impossible given the proximity of this donor site to the head and neck. The bone of the lateral scapula is technically difficult to harvest, given the array of muscular origins on the scapula, making a surgeon's early experiences with this flap relatively difficult. If the teres major and subscapularis are not properly repaired, patients may have considerable problems with shoulder strength and range of motion post-operatively. The pedicle of the scapular flap, particularly when a bone segment based on the nutrient artery is harvested, can be relatively short as the bone branch from the circumflex scapular artery is relatively close to its origin. The available bone is relatively short – 10–12 cm in an adult male – making it less than ideal for hemimandibular or extended resections of the mandible. The skin of the back, while ideal in terms of colour, has a relatively thick dermis and dense subcutaneous fat, making it an inflexible

reconstruction for defects requiring contour changes such as floor of mouth, tongue and palate reconstruction.

TECHNICAL NUANCES

The most important technical nuance for the harvesting of this flap is appropriate patient positioning. One approach is to position the patient on a 'bean-bag', essentially a polyethylene bag filled with beads. When the air is removed from the bag the beads form a firm structure that maintains the patient in the appropriate position. The patient is usually turned 20–30 degrees from the supine position so that the medial border of the scapula is visible and palpable.

Harvesting of the flap requires a detailed understanding of the muscular anatomy of the region. The location of the pedicle within the triangle bordered by teres major, teres minor and the long head of triceps is an important concept to understand. Identifying these structures during the harvest allows easy visualization of the perforators to the skin island. Perhaps one of the more difficult aspects of this flap is the bone harvest and position of the osteotomies. The key is to identify the bone nutrient artery just below the inferior tip of the glenoid. Make a transverse osteotomy between the inferior lip of glenoid and the entry of the nutrient artery into the lateral border of the scapula. The lateral border is then detached by making a vertical cut along the long axis of the scapula medial to the crest or the point of insertion of the teres major, teres minor and the subscapularis. We routinely drill holes in the remaining lateral border of the scapula and carefully reattach the teres major and subscapularis muscles, to maximize recovery of shoulder function.

CLINICAL APPLICATIONS

Cutaneous flap

The cutaneous scapular or parascapular flap has a wide variety of applications in head and neck reconstruction. Because of its colour match, it is ideal for defects of the lateral face, neck and temporal bone. The flap can be de-epithelialized for recontouring of facial defects and a number of authors have described its use for facial recontouring for conditions such as Romberg's disease[33] or secondary deformities of the lateral face. The latissimus dorsi myocutaneous flap has a similar range of reconstruction and is ideally suited for extensive defects of the lateral neck, and has been widely used as a muscle-only flap for scalp reconstruction.[34] The flap has been widely used for oral cavity reconstruction, particularly for composite defects, but the thickness of the dermis and the fat density of the flap make it a less than ideal reconstruction for this defect.

Osseocutaneous flap

The osseocutaneous versions of this flap have a variety of applications in head and neck reconstruction. The bone length available of 10–12 cm limits the use of this flap in extensive mandibular defects, but is adequate for the majority of ablative defects encountered (**Figure 93.8**). The bone is relatively easy to osteotomize, usually with osteotomies of one cortex and then 'green-sticking' the scapula to contour it to the appropriate shape. One of the unique aspects and applications of this flap are in defects including oral lining and external skin cover. The flexibility of the flap allows at least two separate skin islands that can rotate independently of the bone segment. Numerous authors have described the use of the scapular flap in midface and maxillary reconstruction. Two bone flaps are available for this application; the classic scapular bone flap based on the nutrient artery arising from the circumflex scapular artery and the tip of scapular flap based on the angular artery. The former has the limitation of a relatively short vascular pedicle, making its application in midface reconstruction relatively problematic. The tip of scapula based on the angular artery has the advantage of an extremely long vascular pedicle, making it ideally suited for maxillary and midface reconstruction.

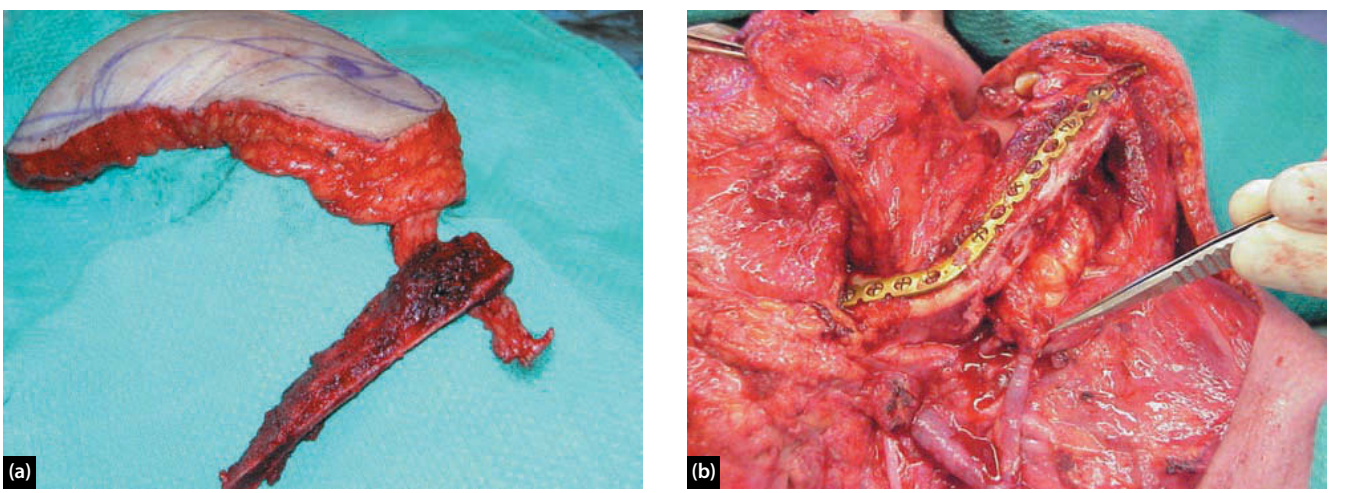

Figure 93.8 (a) Osseocutaneous scapular flap; note thickness of skin and short vascular pedicle. **(b)** Osseocutaneous scapular flap following inset for reconstruction of mandibular body and mucosal lining.

FLAPS FROM THE ABDOMINAL WALL AND PELVIS

Rectus abdominus and deep inferior epigastric artery perforator flaps

The rectus abdominus flap has been a 'workhorse flap' for head and neck reconstruction over the past 30 years. Originally popularized for breast reconstruction as a local myocutaneous flap based on the superior epigastric vessels, it has remarkable utility for head and neck reconstruction. The flap can be harvested as a myocutaneous or perforator-based flap, offering a wide variety of cutaneous or myocutaneous options.[35, 36]

ANATOMY

The rectus abdominus flap is based on the deep inferior epigastric artery and its venae comitantes (**Figure 93.9**). The deep inferior epigastric artery arises from the external iliac artery immediately above the inguinal ligament. It ascends in a lateral to medial direction penetrating the transversalis fascia below the arcuate line, then travelling superiorly between the rectus muscle and the posterior rectus sheath. The artery generally divides into a number of large branches just below the umbilicus, providing numerous perforating branches to the rectus abdominus muscle and the overlying skin. Pedicle lengths from origin to insertion into the muscle range from 8 cm to 14 cm with average vessel diameters of 2.0–3.0 mm. The flap has its sensory and motor supply from the lower six or seven spinal thoracic nerves, making its innervation segmental and less than ideal for functional reconstruction or restoration of sensation.

ADVANTAGES

The rectus abdominus myocutaneous flap or deep inferior epigastric perforator (DIEP) flap has a number of advantages for head and neck reconstruction. The vascular anatomy of the flap is extremely consistent, making it a relatively simple flap to harvest. The ability to transfer a skin/muscle flap, a perforator-based skin flap or a myogenous flap speak to its versatility. Large areas of skin are available, with the majority of defects amenable to primary closure. The donor site is not problematic for males or females and in some patients may offer the aesthetic benefit of an abdominal lipectomy. In most situations the selection of this flap for reconstruction offers the opportunity for a two-team procedure with flap harvest occurring simultaneously with tumour ablation.

DISADVANTAGES

The major disadvantages of this flap relate to donor site issues and the nature of the subcutaneous fat associated with this flap. The most frequent complication associated with this flap is central abdominal hernias, particularly when portions of the anterior rectus sheath are harvested below the arcuate line. The move to the use of more perforator based rectus flaps, which spare the rectus muscle and the majority of the anterior sheath, have certainly reduced the rates of donor site complications. The body habitus of

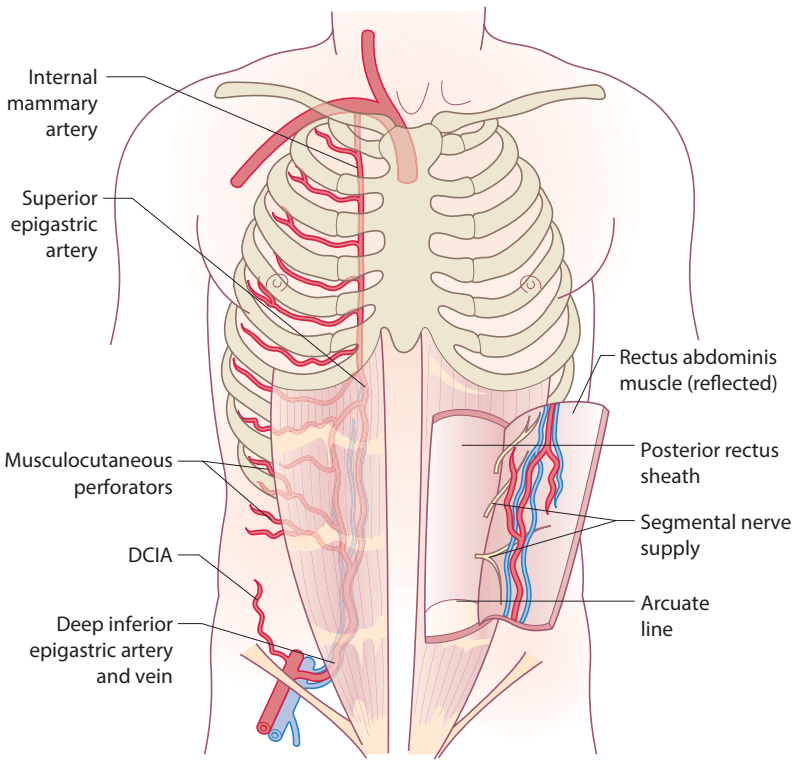

Figure 93.9 Anatomy of the rectus abdominus flap. Redrawn from Ref. 21, with permission.

the patient will determine the tissue match to defects of the head and neck. In obese patients the volume of subcutaneous fat may be inappropriate for defects of the lateral face and neck. In addition, as patients gain weight peri-operatively, the subcutaneous fat will gain volume in proportion to its usual location. These patients may require secondary procedures to reduce the volume of fat in the reconstruction. The colour match to the face and neck is relatively poor with the rectus flap, particularly in Caucasian patients.

TECHNICAL NUANCES

The technical nuances with this flap are largely about reducing donor site complications. The key to minimizing donor site problems is to take as small a piece of the anterior rectus sheath as possible and in particular attempt to avoid taking the anterior sheath below the arcuate line (as there is no posterior sheath). The perforators to the skin of the anterior abdominal wall exit the anterior rectus sheath in an arc around the umbilicus. Most flaps are designed with the base just below the umbilicus where the density of perforators is the greatest. In order to have a viable flap the only fascia that needs to be removed is that which immediately surrounds the perforators themselves. A small narrow strip of anterior fascia is all that should be taken, preserving the remainder for closure. The dissection for the myocutaneous flap begins laterally over the rectus sheath with dissection medially until one identifies the major perforators in the periumbilical region. The anterior sheath is then incised at this point, with a small island of fascia overlying the rectus abdominus muscle with the incorporated skin perforators. The entire rectus muscle is then harvested in a retrograde fashion with the pedicle identified on the deep lateral surface of the muscle, with dissection carried down to the vascular origin. In the DIEP harvest, the surgeon selects a major perforator then follows it through the muscle to the deep inferior epigastric artery (**Figure 93.10**). The lateral aspect of the muscle is identified and lifted medially to facilitate the dissection of the pedicle. The flap is harvested by delivering the vascular pedicle through the muscle, preserving the majority of the rectus abdominus muscle and the anterior rectus sheath.[37, 38] Careful and precise closure of the donor site is critical to avoid abdominal hernia. Where the anterior sheath cannot be closed primarily, reconstructive mesh should be used to avoid hernia formation.

CLINICAL APPLICATIONS

The rectus abdominus myocutaneous flap has been widely used in head and neck reconstruction. Its major applications have been in large volume reconstructions of the oral cavity or oropharynx and lateral skull base. The volume of tissue and the combination of muscle and skin offer the reconstructive surgeon the ability to fill surgical dead space and protect critical structures such as the carotid sheath or dural repairs. The flap is particularly useful for the total glossectomy defect where the volume of tissue can fill the space under the mandible, reducing the risk of perioperative fistula and infectious complications. The perforator-based DIEP flap extends the use of this flap, as the ability to harvest a large cutaneous flap, without the associated muscle, makes it useful for total glossectomy and extensive tongue defects. The DIEP flap can also be used to cover extensive facial and neck defects and may be used to recontour soft tissue defects of the lateral face.

Deep circumflex iliac artery osseomyocutaneous and the myo-osseous flap

The deep circumflex Iliac artery osseomyocutaneous, myo-osseous or osseous flap has the been a 'workhorse' flap for composite defect reconstruction of the oral cavity and mandible since its description by Taylor in 1982.[39]

ANATOMY

The iliac crest transfer is based on the deep circumflex iliac artery and its venae comitantes (**Figure 93.11**). The deep circumflex iliac artery (DCIA) arises from the lateral aspect of the external iliac artery, just above the

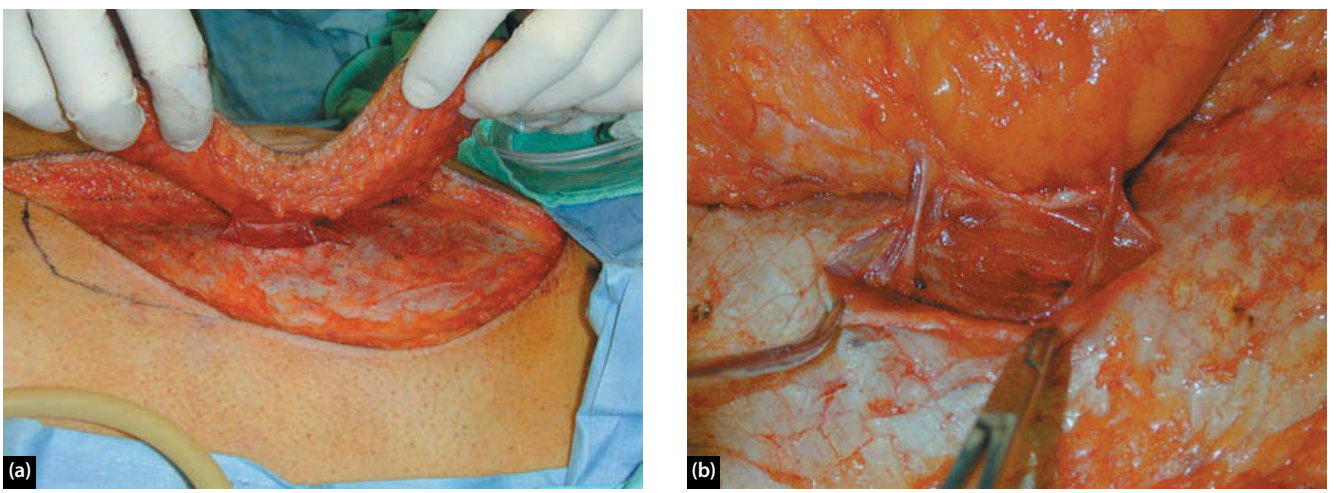

Figure 93.10 (a) DIEP perforator flap; note two dominant perforators and small fascial incision; **(b)** magnified view.

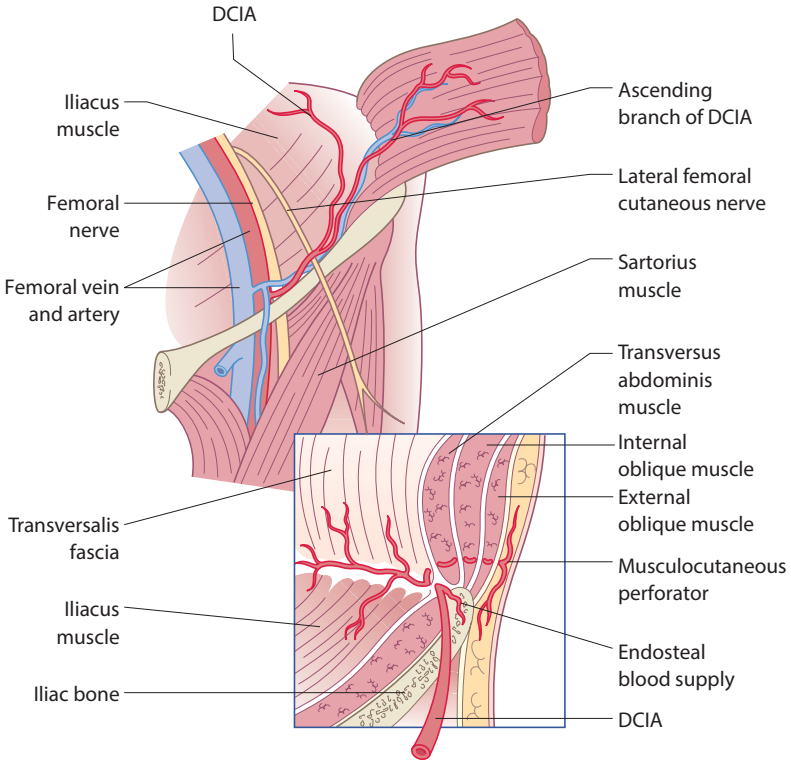

Figure 93.11 Anatomy of the DCIA flap. Redrawn from Ref. 21, with permission.

inguinal ligament. It runs a course parallel to the inguinal ligament, and 1 cm medial to the anterior superior iliac spine it gives off a large ascending branch that pierces the transverses abdominus muscle to lie on the deep surface of the internal oblique. The deep circumflex iliac artery (DCIA) then penetrates the transervsalis fascia and lies along the inner aspect of the crest, about 2 cm below the surface of the crest in the line of fusion of the iliacus and transveralis fascia. The artery extends posteriorly along the crest and about the midpoint of the crest, where it re-enters the transversus abdominus to anastomose with iliolumbar and superior gluteus arteries. Along its course it provides perforating branches that traverse all layers of the musculature of the abdominal wall just above the crest and supply the overlying skin. The venous drainage of the flap is the deep circumflex iliac vein (DCIV) which runs as a venae comitantes but often courses superiorly prior to its drainage into the internal iliac vein. There is some variability in vascular anatomy. The anterior branch may arise from a separate independent pedicle, originating just below the DCIA. The vascular pedicle is 6–8 cm in greatest length, with the artery and vein usually being of large calibre (2–3 mm).

ADVANTAGES

The DCIA-based iliac crest is an ideal flap for reconstruction of the mandible. It can be shaped to recreate both the mandibular body and the vertical ramus. The bone stock is excellent, in terms of both its corticocancellous proportions and the vertical height and breadth of the available bone. The physical properties of the crest make it ideally suited for primary or secondary osseointegration. This flap, when transferred with the internal oblique, provides an excellent vascularized reconstruction for patients with osteoradionecrosis.

DISADVANTAGES

The major disadvantages of the flap relate to the reliability of the skin paddle, the character of the skin paddle and secondary problems with the donor site. The skin paddle associated with the flap needs to be based on the line of the crest. While this makes an ideal skin closure in terms of scar location, in order to harvest a reliable skin island, a cuff of muscle that includes all three muscular layers of the abdominal wall must be retained in order to preserve the perforating vessels. This results in a relatively thick and inflexible reconstruction, making this version of the flap less than ideal for most head and neck applications. The skin flap is notoriously unreliable based on the fragility and unpredictability of the perforator supply. The donor site is problematic, as a significant number of patients will have either frank hernia formation or chronic laxity of the lower abdominal wall. While the lateral cutaneous nerve of the thigh can be preserved in the majority of dissections, in some situations it must be sacrificed, leaving an area of numbness on the lateral thigh. The donor site is painful, particularly when the entire crest is harvested, and peri-operative mobilization can be an issue, particularly in elderly patients. The pedicle length can be problematic when the flap is used for maxillary reconstruction, and vein grafting may be required.

TECHNICAL NUANCES

The DCIA flap is one of the more technically difficult flaps to harvest. Patient positioning is quite important in order

to allow visualization of the medial aspect of the crest. In most iliac crest bone graft harvests, a bag is placed under the hip to rotate it away from the surgeon. In the DCIA flap the surgeon must be able to visualize the medial crest and therefore the reverse position is most appropriate. One approach is to place a soft roll under the sacrum to elevate the pelvis and then rotate the operating table towards the surgical side to maximize visualization. Most experienced microsurgeons try to avoid the osseocutaneous version of the flap because of the unreliability of the flap. Likely the most commonly harvested version of the flap incorporates the internal oblique as a myosseous flap. The pedicle in this harvest is most easily identified by finding the anterior branch of the DCIA on the deep side of the internal oblique and then dissecting in a retrograde fashion to the DCIA. One option to reduce donor site complications is to harvest only the inner table, splitting the crest by making an oblique cut through the top of crest extending just below transversalis reflection. This technique provides adequate bone for mandibular reconstruction and preserves the lateral crest and anterior iliac spine. If one harvests the internal oblique, most surgeons routinely repair the defect with a surgical mesh to avoid abdominal wall laxity.

CLINICAL APPLICATIONS

The DCIA flap is largely used for bone only or composite defects of the mandible or maxilla. Taylor described the DCIA for hemimandibular reconstruction, and numerous series have demonstrated its efficacy for this application.[40, 41] Bone length to be harvested ranges from 8 cm to 12–14 cm, making it useful for the majority of defects encountered. Currently, most authors use this flap as a myo-osseous flap, using the internal oblique to close the oral defect with and either skin grafting of the muscle or allowing it to mucosalize secondarily (**Figure 93.12**).[42]

Most recently, Brown[43] has described the use of the iliac crest transfer for maxillary defects. The flap can be used for premaxillary and infrastructure by turning it horizontally to replace the hard palate. The mucosal defect is not reconstructed but rather the surface of the bone is allowed to granulate and secondarily mucosalize. In classic maxillary defect, the crest is inverted with the vascular pedicle oriented towards the maxillary tuberosity. The muscle is then rotated into the defect and allowed to mucosalize secondarily to recreate the hard palate (**Figure 93.13**). These two flap orientations both allow secondary osseointegration for dental restoration with a thin mucosalized reconstruction of the hard palate.

The anterolateral thigh flap

The anterolateral thigh flap is a fasciocutaneous flap based on the musculocutaneous and septocutaneous perforators of the descending branch of the lateral circumflex femoral artery and its venae comitantes. This flap's surgical anatomy and clinical use were first reported by Song et al.[44] in 1984. In 1989 Koshima et al.[45] described its use in the Japanese population, and numerous subsequent reports have described its successful use in head and neck reconstruction in the Asian population. It has gained popularity in oral cavity reconstruction, particularly in the Asian population, whose body habitus is ideally suited to the use of this flap.[46]

ANATOMY

The anterolateral thigh flap is supplied by perforating vessels arising from the descending branch of the lateral circumflex femoral artery. The descending branch runs downward in the intramuscular space between the rectus femoris and the vastus lateralis, terminating in the vastus lateralis just above the knee (**Figure 93.14**). In the midportion of the lateral thigh, the descending branch provides a number of perforators to the skin of the lateral thigh. These perforators can either run between the rectus femoris and vastus lateralis muscle then traverse the fascia lata as septocutaneous perforators to supply the skin of the lateral thigh or they can traverse the vastus lateralis muscle and the deep fascia as musculocutaneous perforators to supply the skin. The length of the pedicle ranges from 8 cm 16 cm.

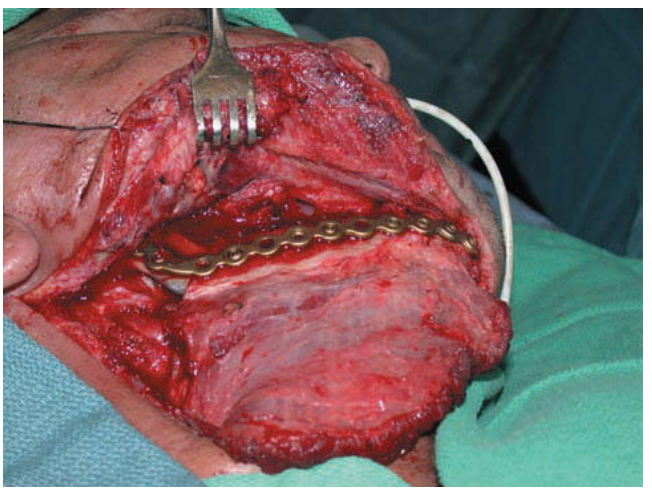

Figure 93.12 DCIA myo-osseous flap; note available muscle for intraoral closure.

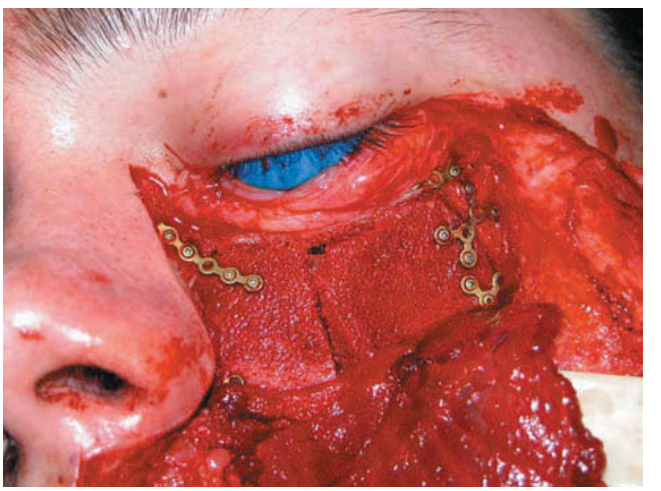

Figure 93.13 Split DCIA for maxillary and orbit reconstruction.

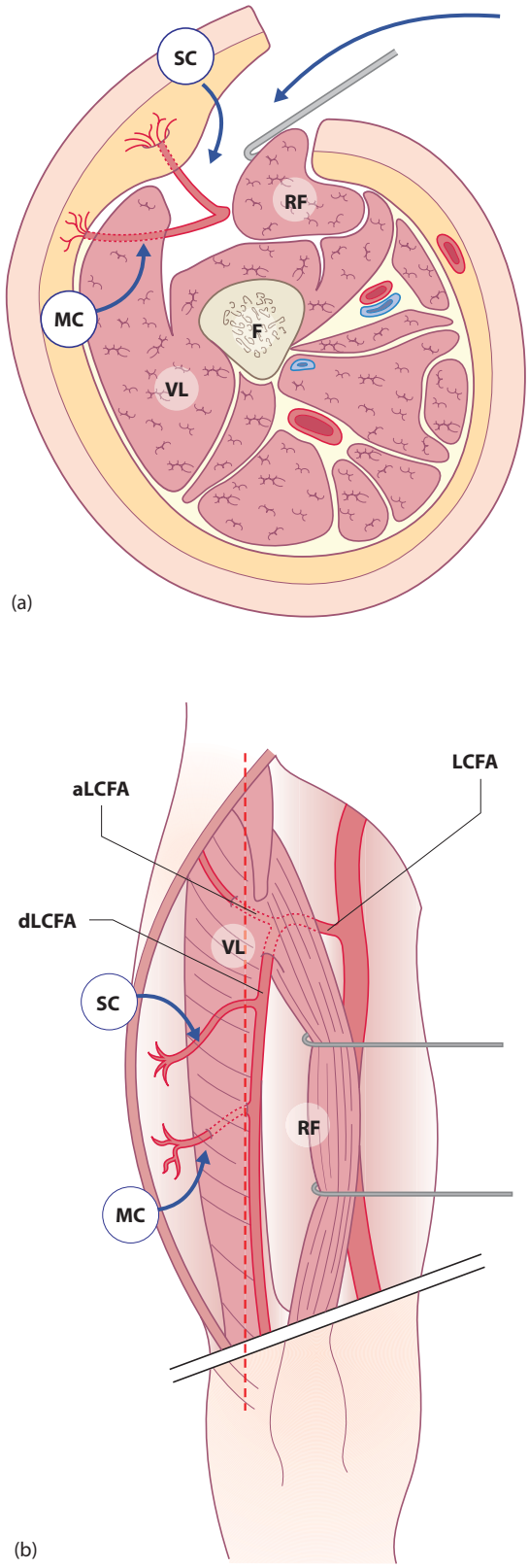

Figure 93.14 Anatomy of anterolateral thigh flap: (a) axial view; and **(b)** coronal view. aLCFA, ascending lateral circumflex femoral artery; dLCFA, descending lateral circumflex femoral artery; LCFA, lateral circumflex femoral artery; MC, myocutaneous perforator; RF, rectus femoris; SC, septocutaneous perforator; VL,vastus laterialis. Redrawn from Ref. 48, with permission.

ADVANTAGES

The anterolateral thigh has a number of advantages for head and neck reconstruction. The flap has a distant site from the head and neck, allowing a two-team harvest. The donor site has limited morbidity and in most patients can be closed primary, in a vertical line. Provided the nerve to vastus lateralis is preserved, little functional disability is associated with this flap. Large skin islands measuring 15–20 cm × 10 cm may be harvested and closed primarily. The flap may be harvested as a perforator flap with or without the fascia lata and can incorporate the vastus lateralis if a muscle component is required. In patients with the appropriate body habitus this flap is thin and pliable and provides an excellent reconstruction for the oral tongue and floor of mouth.

DISADVANTAGES

The anterolateral thigh flap has some disadvantages. The skin colour match to facial and neck skin is poor, especially in Caucasian patients. The anatomy of the flap is variable and somewhat unpredictable so; the surgeon contemplating the use of this flap needs to understand the basic anatomic variations and be prepared for them. Since the cutaneous version of this flap is usually supplied by a single perforating vessel, proximal venous occlusions are usually difficult to salvage because of the small calibre of the perforating vessels. In addition, because of the small size of the perforating vessels, the flap pedicle may be easily compromised by external compression. This makes it a poor choice for reconstructions requiring tunnelling of the pedicle. In some ethnic populations the thickness of fat in the lateral thigh makes this a poor donor site as the volume and bulk of the flap will produce an unreliable flap and a poor functional result.

TECHNICAL NUANCES

The skin perforators of the lateral thigh are mapped with Doppler, using the midpoint of a line drawn between the anterior superior iliac spine and the lateral aspect of the patella as a landmark. The first skin incision is placed on the medial aspect of the flap design. If a suprafascial technique is to be used for a thin flap, the dissection is carried laterally until the major perforators to the skin are identified. If a fasciocutaneous harvest is planned, the incision is carried through the deep fascia with the flap site mobilized laterally until the perforating vessels are visualized traversing the deep fascia. Once the perforators are identified, the skin incisions are completed. The pedicle is dissected in a retrograde fashion, either to the descending branch for septocutaneous flaps or through the vastus lateralis in patients with myocutaneous perforators. In myocutaneous perforators, a small cuff of muscle is left around the pedicle to protect the small perforating branches. Great care should be used to maintain haemostasis in this portion of the elevation because the vessels frequently will go into spasm and the muscle may bleed excessively after revascularization.

CLINICAL APPLICATIONS

The anterolateral thigh flap in appropriately selected patients is ideally suited to a variety of defects in the head and neck. It matches the reconstructive capabilities of the forearm flap, particularly if the thigh is thin and pliable. It can be tubed to reconstruct a tubed conduit for total pharyngeal reconstruction and can be used for external defects anywhere in the head and neck.[47] The donor site is much more attractive than the forearm flap and hence the reasons for this flap replacing the forearm as the standard reconstruction for the oral cavity in Asian countries.

The free osseocutaneous fibular flap

The free osseocutaneous or osseous fibular flap was first described by Taylor[48] for the reconstruction of tibial pseudarthrosis. This flap was popularized by Hidalgo and Rekow[49] for mandibular reconstruction and currently represents the benchmark for composite defects of the mandible and oral cavity.

ANATOMY

The osseocutaneous fibular flap is based on the peroneal artery and vein (**Figure 93.15**). The peroneal artery is a branch of the tibioperoneal trunk. The artery passes distally with paired venae comitantes lying on the medial aspect of the fibular between the tibial posterior and the flexor hillocks longus. The peroneal artery provides perforating branches to the surrounding musculature and nutrient artery and periosteal supply to the fibula. In the distal half of the leg it gives off perforating branches that run laterally through the flexor hallucis longus, usually passing within or deep to the intermuscular septum separating the peroneus longus and soleus muscles (**Figure 93.16**). The skin available includes the majority of the surface of the lateral aspect of the lower leg, with flaps measuring 12–16 cm × 8–10 cm available. The length of bone available is usually 18–24 cm depending on the length of the leg. Pedicle length depends on the amount of bone required (longer bone lengths = shorter pedicle) The usual vessel diameter is 3–4 mm for the artery and 4–5 mm for the vein.

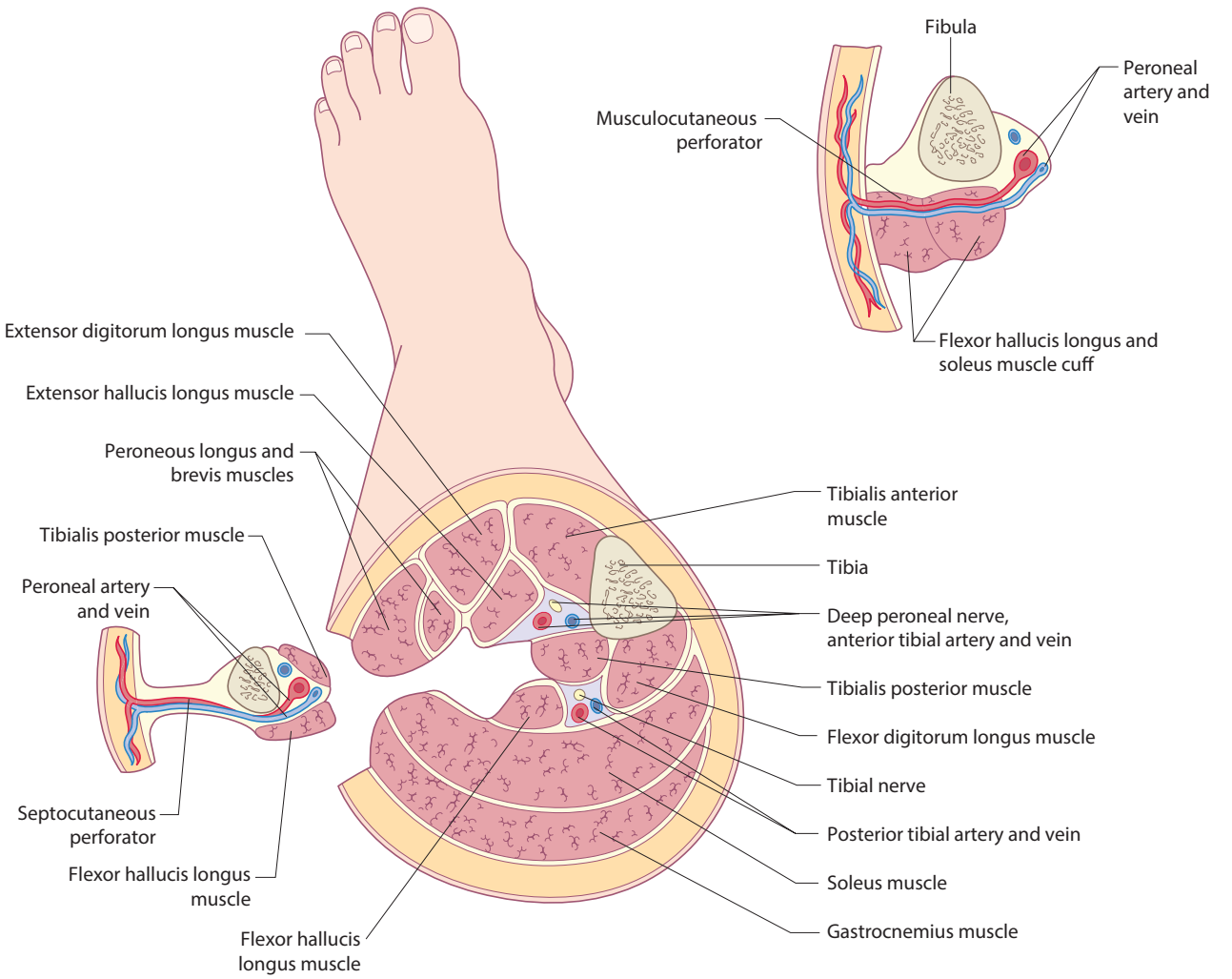

Figure 93.15 Anatomy of the free fibular transfer. Redrawn from Ref. 21, with permission.

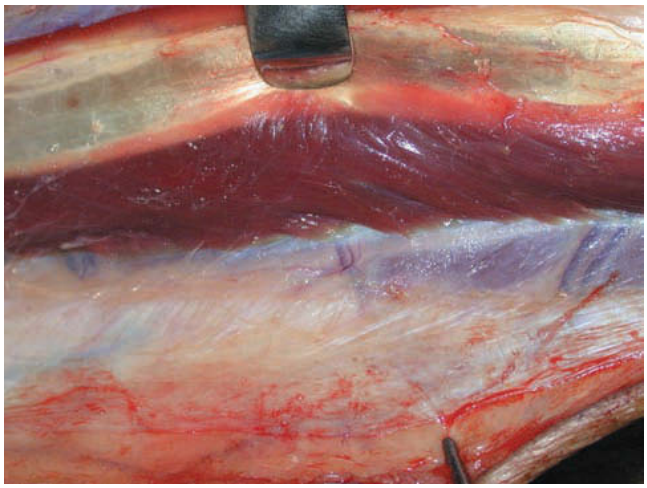

Figure 93.16 Lateral view of perforators to fibular skin paddle; note peroneous longus anteriorly and three septocutaneous perforators running to the skin island.

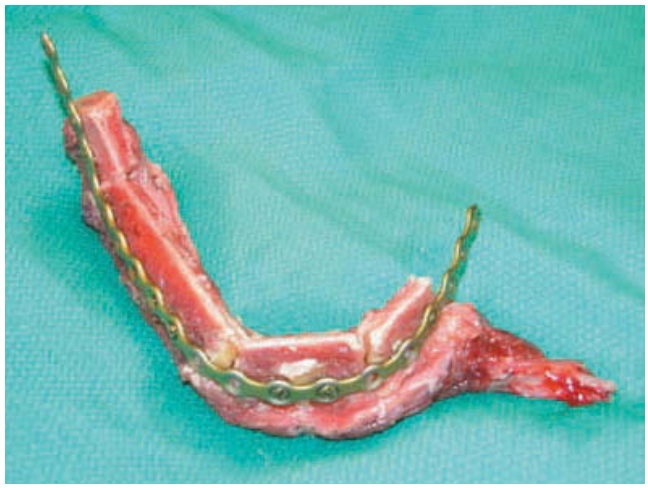

Figure 93.17 Osteotomized fibula, for mandibular reconstruction; note the use of a low profile reconstruction plate.

ADVANTAGES

The fibula is an ideal transfer for the majority defects of the oral cavity and mandible. The bone length available will almost reconstruct the entire mandible. The skin island is of an appropriate thickness for most oral cavity and oropharyngeal reconstructions.

DISADVANTAGES

The fibula has some established liabilities. It is not a good option in individuals with established peripheral vascular disease as harvesting a single vessel in an arterially comprised leg could be catastrophic. Some authors have reported relatively high failure rates with the skin island. These can be reduced with particular attention to harvest technique as outlined below.[50] The donor site can be problematic in patients with venous insufficiency in the lower extremity, with delayed healing of skin graft sites. Some patients have reported long periods of ankle and leg stiffness and occasional instability of the ankle. If a large cuff of flexor hallucis is harvested with the flap, some patients will acquire a flexion deformity of the great toe.

TECHNICAL NUANCES

As in all free tissue transfers, surgical planning is paramount to avoid complications. Most authors routinely advocate some type of non-invasive imaging of the vascular anatomy of the leg and tibioperoneal trunk. Options include colour Doppler, magnetic resonance angiography (MRA) and computed tomographic angiography (CTA). Experienced surgeons routinely Doppler the perforating branches to the skin to ensure that the skin island is appropriately placed on the leg. The flap is usually harvested under tourniquet control to provide a dry surgical field. Current harvest technique is usually via the lateral approach. After incising the skin island the peroneous longus and brevis are reflected anteriorly off the fibula. The anterior compartment is entered and opened over the length of the fibula, avoiding the anterior tibial artery. The posterior interosseous membrane is divided, visualizing the tibialis posterior. The fibula is divided distally and proximally, leaving at least 6 cm of fibula at the ankle and knee to avoid instability of the ankle and prevent injury to the common peroneal nerve. The distal peroneal artery is divided; the tibialis posterior is divided, visualizing the full course of the peroneal artery. To avoid injury to the perforators to the skin and assure appropriate venous drainage of the skin flap most authors advocate harvesting a cuff of flexor hallucis longus and soleus. Pedicle length is established by detaching the peroneal artery from the fibula. Closure is achieved either primary or with a skin graft. Most authors splint the leg for 5–7 days to maximize skin graft take.

The fibula may be osteotomized into multiple segments to recreate the shape of the mandible. Most authors currently use a single reconstruction plate lagging the bone segments to the plate while others prefer using multiple small plates to recreate the mandible. It is our preference to generally harvest the fibula from the leg contra lateral to the mandibular defect, as this positions the pedicle in the appropriate location for recipient vessel access and keeps the skin island in the right orientation for insetting into the oral defect. If the skin island has to be rotated around the fibula to get into the oral cavity the perforating vessels to the skin may be compromised, resulting in loss of the skin flap.

CLINICAL APPLICATIONS

The fibular flap is widely used for oromandibular reconstruction and is ideally suited for this defect (**Figure 93.17**). The bone flap is relatively short in vertical height, often leaving a disparity between the natural bone height of the mandible and the reconstructed segments. Some authors have advocated 'double-barreling' – placing one segment on top of the other to maximize vertical height for secondary osseointegration.[51] This flap has been used for maxillary reconstruction and is ideal for reconstructing the premaxilla in central maxillary defects. The other advantage of this flap for maxillary reconstruction is the

potential length of the vascular pedicle, a major asset in midface reconstruction.

ENTERIC RECONSTRUCTIONS

The free jejunal transfer

The free jejunal transfer, described by Seidenberg and Hurwitt[52] in 1958, has been widely used for conduit reconstruction of pharynx over the past 30 years. Numerous large series report success, in terms of both reliability and functional outcomes.[53, 54]

ANATOMY

The jejunum comprises approximately two-fifths of the 7-metre length of small bowel extending from the duodenum to the ileocecal valve. The blood supply of the jejunum arises from approximately five branches arising from the superior mesenteric artery with a total of 12 to 15 branches to the jejunum and ileum. The vessels run parallel to each other between the mesenteric layers. Each vessel divides into two, forming a series of arcades. From the terminal arcade, numerous vasa recta pass to the mesenteric border of the jejunum. Jejunum of 10–20 cm may be harvested with pedicle lengths of up to 8–10 cm. The artery is usually 1.5–2.5 mm in diameter with a matching venae comitantes. The vein can be extremely thin and technically difficult to sew.

ADVANTAGES

The jejunum is a mucosal lined conduit that makes its own secretions, making it theoretically an ideal reconstruction for a total pharyngectomy defect. The length of jejunum available for harvest is adequate for any head and neck defect. The jejunum has a peristaltic wave, which is unidirectional and can assist in swallowing

DISADVANTAGES

The jejunum has some problematic disadvantages. The flap does not tolerate long periods of ischemia and like other intestinal conduits does not tolerate long periods of venous congestion. The flap must be oriented in the appropriate direction or patients may be unable to swallow. The swallowing characteristics of this flap are highly variable. Some patients find that the flap easily goes into spasm with ingestion of hot or cold liquids and most patients describe swallowing as adequate but slow. One of the major drawbacks of the jejunum for pharyngeal reconstruction is that secondary tracheo-oesophageal puncture (TEP) speech is patulous and wet, with the majority of patients preferring not to use a TEP. The swallowing and speech results seem to be improved in patients who have received post-operative radiotherapy reducing the contractility and inherent secretions of the jejunum. Because the flap is enteric in origin it does not develop collateral circulation from the surrounding tissues. The pedicle of this flap can never be divided without risk of conduit necrosis, even after being in place for many years.

TECHNICAL NUANCES

The flap is usually harvested with a mini-laparotomy or endoscopically. The jejunal segment is delivered up onto the abdominal wall and the arcades visualized with back lighting. Usually the second intestinal branch is harvested with the segment of jejunum it supplies. Most surgeons harvest more length than needed so that a segment of the mesentery is available to place through the skin incision as an external monitor. Insetting of this flap is critical. It must be placed in an isoperistaltic position to allow swallowing. Most authors advocate marking the distal or proximal ends with a suture to avoid confusion about the direction of inset. The jejunum must be stretched to fit the defect as much as possible as, once it is revascularized, its length will increase, producing a tortuous conduit that functions poorly for swallowing.

CLINICAL APPLICATIONS

The most common application for jejunum is the total laryngopharyngectomy defect (**Figure 93.18**). Some authors have used it as a mucosalized and self-lubricating flap for oropharyngeal reconstruction, particularly in the radiation failure patient where xerostomia may be a problem. This technique can be problematic as the jejunal secretions are often tenacious and foul smelling.

The free gastro-omental flap

The free gastro-omental flap was described by Baudet et al.[55] in 1978. This flap has seen limited use over the past 30 years, with limited reports of use for oral cavity and conduit reconstruction of the total laryngopharyngectomy defect.[56]

ANATOMY

The greater curve of the stomach and the omentum are supplied by the right and left gastroepiploic arteries, terminal branches of the gastroduodenal and splenic arteries, respectively. They course along the greater curvature of the stomach and anastomose with each other, forming the gastroepiploic arterial arch. From the gastroepiploic arch,

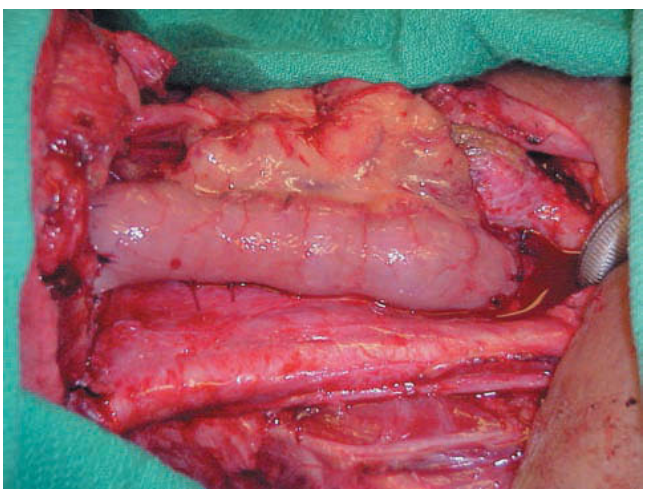

Figure 93.18 Free jejunal transfer for pharyngeal reconstruction.

numerous small branches extend to the greater curvature and three major omental arteries, the right, middle and left, supply the greater omentum. The right gastroepiploic artery is the dominant supply (**Figure 93.19**).

ADVANTAGES

The free gastro-omental flap as a tubed conduit represents a near ideal reconstruction for the laryngopharyngectomy defect, particularly in an era of organ preservation approaches incorporating chemotherapy and radiation. The flap can be customized to tube size, is self-lubricated and not motile. The major benefit of the flap is that it is harvested with a large segment of the greater omentum, providing valuable well-vascularized tissues to cover the carotid sheath and prevent wound complications. The limited reports of its use in total pharyngectomy reconstruction have indicated that the TEP speech is better than with the jejunal transfer.

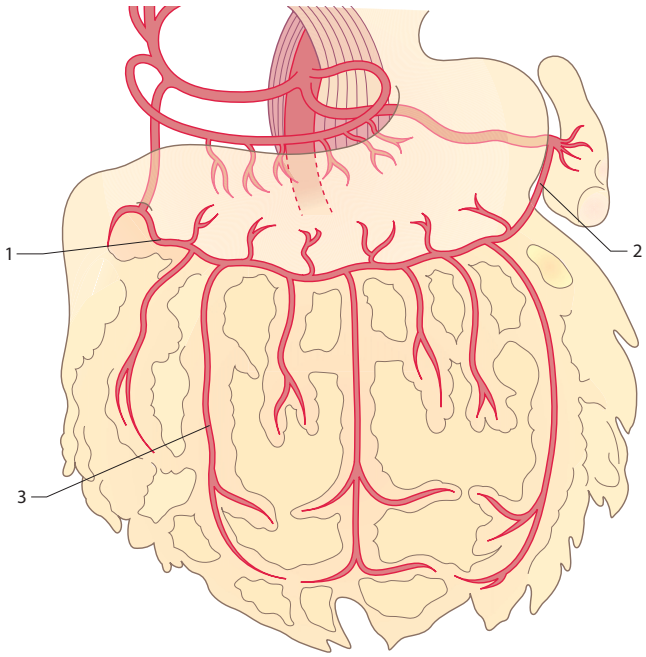

Figure 93.19 Surgical anatomy of the gastroepiploic flap. 1, Right gastroepiploic artery; 2, left gastroepiploic artery; 3, blood supply to the greater omentum.

DISADVANTAGES

The gastro-omental flap has few disadvantages. It does require a laparotomy, which can be a problem in patients with significant comorbidity or poor performance status. The flap is relatively easy to harvest, with a few caveats as discussed below.

TECHNICAL NUANCES

The flap is harvested through a mini-laparotomy incision. The stomach is delivered and the greater omentum visualized. The lesser sac must be entered to visualize the greater curve completely. A large segment of greater omentum is harvested, which can be reduced in volume after insetting. The stomach tube is created by placing a gastrotomy at least 2–3 cm proximal to the pylorus and an appropriate proximal gastrotomy for the length of stomach required. The gastric tube is formed by placing a 35-gauge chest tube through the gastrotomies and then using a GIA stapler to create the conduit. It is critical that the stomach be stretched out to length before stapling to ensure that enough functional stomach remains. A jejunal feeding tube is placed for patients undergoing laryngopharyngeal reconstruction.

CLINICAL APPLICATIONS

The gastro-omental flap is largely used for conduit reconstruction following laryngopharyngetomy. Its unique advantage is the large segment of greater omentum, which will dramatically reduce the risk of peri-operative complications in chemoradiation failure patients (**Figure 93.20**).

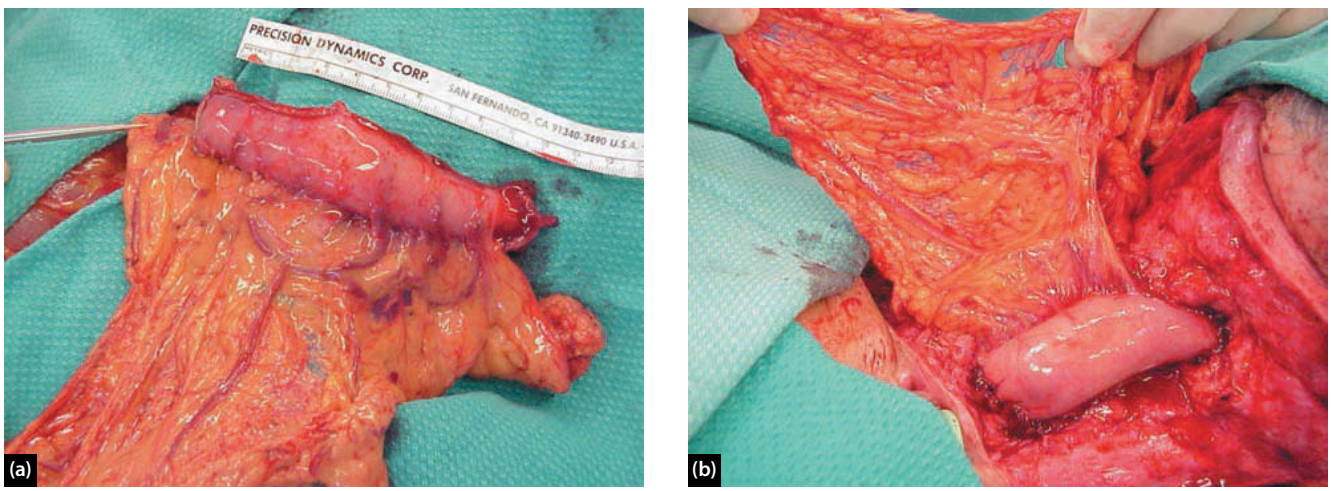

Figure 93.20 (a) and **(b)** gastro-omental flap for oropharyngeal reconstruction; note amount of greater omentum available for resurfacing the anterior neck.

DEFECT-BASED OPTIONS

Oral tongue and floor of mouth

ISSUES

Reconstruction of the oral cavity continues to represent one of the major challenges in head and neck reconstruction. Numerous authors have reviewed functional outcomes following oral cavity reconstruction and have all come to similar conclusions.[57, 58] It would appear that the key element in producing high quality oral function is the amount of sensate tongue remaining in the oral cavity. Any reconstruction used in the oral cavity should have the goal of replacing the volume resected but must maintain and not limit the mobility of the tongue remnant. Highly sensate flaps such as the free forearm flap have been widely used in oral cavity reconstruction, clearly providing two-point, touch and temperature sensation for the reconstructed oral cavity. Intuitively it would seem that sensation would be beneficial but there is little evidence that sensate flaps make a major difference in oral function following ablative procedures. In posteriorly placed defects in the oropharynx, specifically the tongue base and palate, two additional issues are of importance. In tongue base resection, appropriate but not excessive volume replacement appears to improve swallowing results. In soft palate reconstruction, recreating appropriate palate closure is particularly important to avoid nasal regurgitation.

OPTIONS

The current options for oral reconstruction are outlined in **Table 93.1**. The forearm flap has a number of unique advantages. It is thin and pliable, and certainly functions well at maintaining the mobility of the residual tongue. This flap is likely the best sensate flap available and if one believes sensation is important this would be the preferred flap. The anterolateral thigh flap in patients with the appropriate body habitus is likely very close to the forearm in producing high quality functional results. The other flaps available all suffer from providing too much bulk and potentially can limit the residual movement of the oral and oropharyngeal structures.

PROBLEMS

The problems still needing to be addressed in the oral cavity are the production of functional sensation and correcting problems with xerostomia following radiation treatment. The use of the submandibular gland transfer, moving the gland out of the field of radiation, is likely a technique that will be more widely used in the future.[59]

Pharynx

ISSUES

Reconstruction of the total pharyngectomy defect continues to represent one of the major challenges in head and neck reconstruction. The ideal pharyngeal reconstruction would provide a mucosalized conduit that has appropriate motility and functions with a TEP. The reconstruction would be of low morbidity in terms of its donor site, and relatively easy to harvest and revascularize.

OPTIONS

The current options for reconstruction of this defect are the enteric reconstructions; the jejunum or gastro-omental flap or tubed skin flaps. There is extensive experience worldwide with the jejunal flap and it has proven efficacy in the reconstruction of this defect. Swallowing and speech results with the jejunum are less than perfect, which has led some centres to consider the free gastro-omental flap. The gastro-omental flap appears to produce improved swallowing and voice results with the benefit of a large segment of greater omentum.

There have been numerous reports of cutaneous skin tubes for oral reconstruction, in particular the free forearm flap and anterolateral thigh flap. Both these reconstructions have excellent swallowing and voice results, with low donor site morbidity, but have been problematic in the development of distal anastomotic strictures. A number of authors now advocate the use of silastic stents with the cutaneous flaps, an approach that appears to have dramatically reduced the rate of distal anastomotic stricture.

PROBLEMS

The current options in pharyngeal reconstruction appear to be a choice between the improved functional results with enteric reconstructions (particularly the gastro-omental flap) as compared to cutaneous flaps, balanced against the inherent morbidity of the enteric flaps, which

TABLE 93.1 Options in oral cavity reconstruction

Flap	Anatomy	Pedicle length	Sensation	Donor site morbidity	Skin quality
Forearm	+++	+++	+++	++	+++
Lateral arm	++	+	++	+++	++
ALT	+	+++	+	+++	++
DIEP	+++	+++	+	++	++
Scapula	+++	++	+	++	++

+++, best; ++, intermediate; +, poor. ALT, anterolateral thigh; DIEP, deep inferior epigastric perforator.

require a laparotomy. Prospective studies evaluating the long-term functional outcomes of these various reconstructions will help elucidate the best approach for this complex group of patients.

Composite mandibular defects

ISSUES

Reconstruction of composite defects including oral lining and the mandible continue to challenge reconstructive surgeons. In mandibular reconstruction the key issue is the length of bone required, whether the transferred bone is amenable to secondary osseointegration and the morbidity associated with the donor site of the bone flap.

Secondary issues are the correction of disparities in bone height between the native mandible and condylar reconstruction. The mandibular resection that extends to include the condylar head continues to be a problem in terms of recreating a functional joint that will allow an appropriate range of movement for mouth opening and mastication.

OPTIONS

The current options for mandibular reconstruction are illustrated in **Table 93.2**. Currently the flap of choice in most centres is the free fibular transfer based on the quality of the available skin island and the length of available bone with limited donor site morbidity. The scapular bone flap is likely an excellent option where the fibula is not an option because of peripheral vascular disease and is particularly useful in the elderly. The DCIA flap has great utility in limited defects in younger patients. The osseocutaneous radius transfer has a limited bone stock and significant potential donor site problems, making it a poor choice for mandibular reconstruction. A new option for improving functional outcome in mandibular reconstruction has been the developments in computerized assisted design with three-dimensional planning of defect creation and reconstruction. In the most advanced form of this technology, surgeons are supplied with a pre-bent reconstruction plate and a cutting guide for both the fibula or scapula and the ablative defect. This technology while currently expensive, offers the opportunity for improved aesthetic and functional outcome, particularly when comprehensive dental reconstruction with osseointegrated implants is an option.

PROBLEMS

The available options for mandible reconstruction largely achieve the goals of reconstruction of this defect. Re-creation of a functional non-prosthetic condyle continues to be a problem and simple surgical techniques to augment the vertical height of the existing mandibular reconstructions would be helpful.

Cutaneous defects

ISSUES

The major issues in selecting a reconstruction of the external skin of the face or neck are the colour match of flap, donor site morbidity and the ability of the defect to match the volume of the defect. There is a wide variation in skin colour based on anatomic regions of the body, with areas close to the head and neck providing the best colour match. In addition there are remarkable variations in the colour of the various skin flaps based on the race and genetic background of the patient.

OPTIONS

There is a wide variety of options for replacement of facial and neck skin. When balancing donor site morbidity with skin colour, amount of available skin and the ability to adjust the volume of the reconstruction, the scapular system of flaps and the anterolateral thigh appear to offer the greatest potential

CONCLUSIONS

Developments in free tissue transfer over the past 30 years have dramatically affected the outcomes for patients with head and neck deformity. As experience develops with the aforementioned reconstructions, the indications and efficacy of the various techniques will be further delineated. The developments over the next decade in tissue engineering and in the management of the immune response to allogeneic transplants will certainly offer further opportunities for better and more functional reconstructions for head and neck patients.

TABLE 93.2 Osseocutaneous flaps for mandibular reconstruction

Flap	Bone length (cm)	Pedicle length (cm)	Donor complications	Osseointegration	Skin reliability
Fibula	16–20	6–8	+++	++	++
Scapula	8–12	4–8	++	++	+++
Iliac crest	10–14	6–8	+	+++	+
Radius	8–12	8–10	+	+	+++

+++, best; ++, intermediate; +, poor.

BEST CLINICAL PRACTICE

- ✓ Free tissue transfers are best performed in centres with high clinical and surgical volumes with specialized nursing units for post-operative management and monitoring.
- ✓ For reconstruction of oral cavity mucosal defects the best options are:
  - ✓ free forearm flap
  - ✓ anterolateral thigh flap
  - ✓ lateral arm flap
  - ✓ DIEP flap.
- ✓ Options in the reconstruction of mandibular defects need to be tailored to the specific defect, bone length, mucosal defect and rehabilitation plan. Current options are:
  - ✓ fibular transfer
  - ✓ iliac crest
  - ✓ scapula
  - ✓ radius.
- ✓ Reconstruction of the total pharyngectomy defect is a balance between ultimate functional requirements and donor site morbidity. Current options include:
  - ✓ cutaneous tubed flaps – forearm flap and anterolateral thigh flap
  - ✓ enteric flaps – free jejunal transfer and free gastro-omental transfer.
- ✓ Reconstruction of large cutaneous defects of the head and neck is a balance between skin colour match, defect size and donor site morbidity. Current options include:
  - ✓ scapular system of flaps including latissimus dorsi
  - ✓ rectus abdominus and DIEP flaps
  - ✓ anterolateral thigh flap
  - ✓ lateral arm flap
  - ✓ forearm flap.

FUTURE RESEARCH

- ➤ Oral cavity mucosal reconstruction, the value of sensation and the options for recreating sensation in the oral cavity. Prospective outcome studies evaluating the efficacy of the various reconstructive techniques in terms of speech and swallowing. Research and creative opportunities in prefabrication of reconstruction and evaluating the utility of allotransplantation.
- ➤ Mandibular reconstruction, deficiencies in prospective evaluations of functional outcomes (swallowing and deglutition). Further definition of the role of osseointegration technology in oral rehabilitation. Prefabrication of mandibular components and evaluating the utility of allotransplantation.
- ➤ Maxillary reconstruction, deficiencies in prospective studies evaluating outcome and quality of life in patients treated with reconstructive procedures or maxillofacial prosthedontics. Further developments in reconstructive options are required.

KEY POINTS

- It is necessary to understand the blood supply of the skin, the angiosome concept.
- There has been recent interest in the terminology and concept of perforator flaps.
- The special considerations for patients undergoing free tissue transfer include:
  - perioperative fluid management
  - deep vein thrombosis prophylaxis.
- There is a need for specialized nursing units for monitoring free tissue transfer to facilitate rapid return to the operating theatre for vessel occlusion. Two techniques used are:
  - fibrinolytics
  - medicinal leeches.
- The forearm flap is the ‘workhorse’ for oral cavity and oropharyngeal defects. Its advantages are ease of harvest, long pedicle length and potential for sensation.
- The lateral arm flap offers limited donor site morbidity with the disadvantage of a short vascular pedicle and small donor vessels.
- The scapular system of flaps includes the latissimus dorsi flap and provides the following options:
  - variety of skin, muscle, bone or combinations of tissues available
  - skin paddle can be rotated independent of the bone flap
  - great utility for extensive head and neck defects.
- The rectus abdominus flap has consistent anatomy and is excellent for large cutaneous, oral or skull base defects. The perforator-based DIEP flap reduces donor site morbidity and broadens the range of use of this flap.
- The DCIA is the ideal bone for mandibular reconstruction. Its disadvantages relate to donor site morbidity and a short pedicle. Recently, a new application in maxillary reconstruction has been described.
- The anterolateral thigh flap is a recently popularized flap, particularly in patients with thin thighs. Advantages are minimal donor site morbidity and long vascular pedicle. It has a wide variety of applications in head and neck reconstruction.
- The fibular flap is the current standard of care for extensive mandibular defects. Care needs to be taken in using this flap in patients with peripheral vascular disease.
- The free jejunal flap has been widely used for total pharyngeal reconstruction. The swallowing results are good but not excellent, and speech rehabilitation with this flap is problematic.
- The gastro-omental flap has seen limited use for pharyngeal reconstruction over the past 30 years. It has become more popular based on the opportunity to transfer large segments of omentum, which may be an advantage in the chemoradiation failure patient.

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CHAPTER 94

BENIGN AND MALIGNANT CONDITIONS OF THE SKIN

Murtaza Khan and Agustin Martin-Clavijo

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SEARCH STRATEGY

Data in this chapter may be updated by a PubMed and Cochrane library search using the keywords: skin cancer, basal cell carcinoma, squamous cell carcinoma, non-melanoma skin cancer, actinic keratosis, Bowen's disease, melanoma, excision margins, incomplete excision, diagnosis, management, guidelines, recurrence, head and neck.

INTRODUCTION

Skin cancer is on the rise. According to the World Health Organisation (WHO), between 2 to 3 million non-melanoma skin cancers (NMSC) and 132 000 melanomas are diagnosed every year,[1] with one in every three cancers being a skin cancer. NMSC incidence is difficult to assess, as these cancers do not need to be reported to most cancer registers. However, it has been estimated that in the US the increase over the last two decades has been threefold, with an 8% yearly increase.[2] In Scotland, between 1990 and 2011, basal cell carcinomas (BCCs) have increased by 260% and squamous cell carcinomas (SCCs) by 334%. In England, the incidence of BCCs was calculated at 76.2/100 000 and SCCs 22.65/100 000.[3] The incidence of melanoma has also risen continuously since the 1950s. In 2012, the incidence was estimated by the WHO at 111 481, accounting for 1.7% of all cancers (excluding NMSC).[4] The incidence is estimated to have been rising by 3–7% yearly for fair skinned Caucasian populations.[5] At the same time, the mortality (reported in the same study at 24 069) seems to be decreasing.[6]

PREMALIGNANT SKIN LESIONS

Premalignant epithelial lesions are associated to an increased risk of transformation into skin cancer and are confined above the dermo-epidermal junction. Almost all of them are induced by excessive, chronic sun exposure.

Actinic keratosis

Actinic keratoses (AKs) or solar keratoses are the commonest premalignant lesions of the skin (**Figure 94.1**). They are intra-epithelial neoplasms formed by proliferation of atypical keratinocytes and have the potential to grow into invasive SCC. They usually appear after 50 years of age. Sun-seeking behaviour, outdoor occupations, chronic use of sun beds, fair skin, high ultraviolet index of the environment, immunosuppression and genetic syndromes such as albinism and xeroderma pigmentosum are important predisposing factors. Ionizing radiation and ultraviolet light phototherapy can also result in the formation of these lesions.

EPIDEMIOLOGY

AKs are frequently found on skin chronically exposed to ultraviolet radiation, with 80% or more presenting on the face, scalp, neck and dorsal hands.[7] Patients with Fitzpatrick skin phototypes I to III (i.e. those with light coloured skin and a tendency to burn) are at higher risk, and those living near the Equator or at higher altitudes have a greater predisposition. Men are more commonly affected than women. The reported prevalence is variable, with 40–50% of the Australian population aged 40 years and over and 11–25% in the US thought to be affected.[8] The risk of transformation to SCC is low for individual lesions but in patients with a large number of AKs the risk is higher than for the general population.

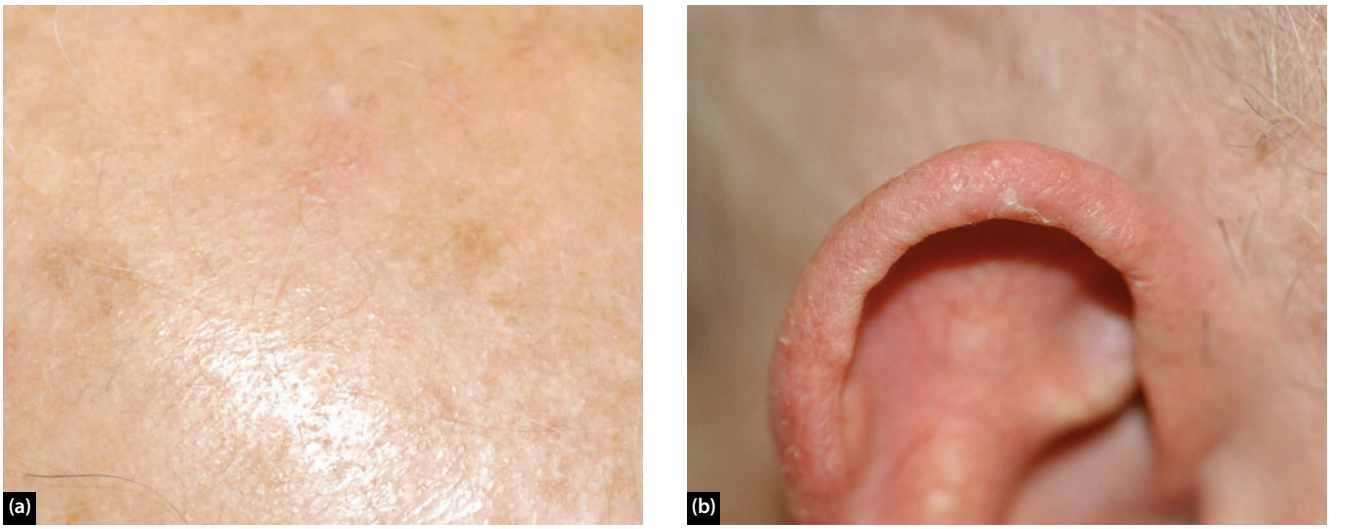

Figure 94.1 Actinic keratosis.

CLINICAL FEATURES

AKs are usually asymptomatic but are noticed because of their rough texture. They appear as dry and erythematous lesions on sun-exposed skin (**Figure 94.1**). Thin lesions are more easily palpable than visible. They are usually covered with an adherent scale. Lesions may be pigmented or telangiectatic and may be numerous. Thicker lesions may have significant hyperkeratosis that can form a cutaneous horn. The surrounding skin often shows evidence of chronic sun damage in the form of wrinkled and atrophic skin, scarring, pigmentation, telangiectasia or changes of solar elastosis characterized by thickened, yellow and wrinkled skin.

DIAGNOSIS

The diagnosis can be made clinically but where there is uncertainty a skin biopsy may be indicated. Features that should raise suspicion of SCC include induration, rapid proliferation, ulceration, bleeding and the presence of a cutaneous horn. Histologically atypical cells confined to the epidermis are seen with increased mitoses, nuclear polymorphism, hyperchromasia and loss of polarization.

The differential diagnosis includes other malignant lesions, such as superficial BCC, Bowen's disease (BD), SCC, amelanotic melanoma and benign lesions such as seborrheic keratosis, viral warts and discoid lupus.

MANAGEMENT

Spontaneous resolution of these lesions has been reported to occur in 21% of cases[9] and for thin and small lesions no treatment may be necessary. In such cases a moisturizer or a keratolytic agent containing salicylic acid may be sufficient to soften the skin. Cryotherapy can be effective for thicker lesions but it is painful and leaves a scar. Topical 5-fluorouracil cream administered once or twice daily for up to 6 weeks can result in clearance with superior cosmetic results but soreness and inflammation during treatment are common. Similar results are achieved with the topical immune response modifier imiquimod used three times a week for 4 weeks with a side-effects profile very similar to that of 5-fluorouracil. Ingenol mebutate has a similar side-effect profile, but has the advantage of needing only two daily applications to treat head and neck AKs. Photodynamic therapy (PDT) with a photosensitizer such as methyl aminolevulinic acid and red light source can be a highly effective treatment, with good overall tolerance and patient satisfaction.[10] Surgery in the form of curettage or excision may be performed when other treatments fail or if there is diagnostic uncertainty.

Prevention is an important aspect of management and advice regarding avoidance of sunlight and tanning beds, protective clothing and regular use of sun blocks should be given. Use of regular sunscreen is the only intervention that can reduce the formation of AKs.[11] Patients should also be taught how to recognize skin cancer and should be prompted to seek medical attention for non-healing and enlarging skin lesions.

Bowen's disease

Squamous cell carcinoma *in situ* or BD was first described by John Bowen in 1912. It is an intra-epidermal carcinoma that involves the full thickness of the epidermis without invading the basal membrane. It persists for many years and can grow, but the risk of progression to invasive SCC is small (3–5%).[12] As with AKs, chronic sun exposure plays an important role in the pathogenesis and immunosuppression predisposes to these lesions. Mucosal BD also occurs[13, 14] and is associated with human papillomavirus (HPV).

EPIDEMIOLOGY

BD is seen more commonly in women than in men. It is usually diagnosed in patients from 60 years of age. Most lesions present on the head and neck[15, 16] but in the UK the distribution is significantly different with only 13% on the head and neck and 67% on the lower limbs.[17] Lesions of

BD are usually solitary but can be multiple. The risk of progression to invasive SCC has been estimated to be around 5%.

CLINICAL FEATURES

Patients present with a long-standing and slowly growing skin lesion, which is usually asymptomatic. It appears as a well-defined, sharply demarcated and scaly erythematous plaque on chronically sun-exposed skin.

DIAGNOSIS

The diagnosis can be suspected clinically but a skin biopsy is recommended to exclude differentials and rule out invasive SCC. Histologically the full thickness of the epidermis shows dysplastic cells with disordered architecture, abnormal mitoses and hyperkeratosis. The abnormal cells do not invade the basal membrane but can sometimes extend along the hair follicle epithelium.

The clinical differential diagnosis of BD includes lichen simplex, eczema, psoriasis, fungal infection and superficial BCC.

MANAGEMENT

Most lesions of BD can be treated by non-surgical methods. As with AKs the use of 5-fluorouracil cream can be a highly effective treatment. Imiquimod cream can achieve similar results and is particularly useful in cases associated with HPV. Cryotherapy using liquid nitrogen with one or two freeze-thaw cycles can be effective but the usefulness of the procedure is limited by pain and slow healing rates and it is often impractical for larger lesions. PDT can achieve cure rates of around 90%.

Surgery may be performed when conservative measures fail or there is suspicion of invasive disease. Curettage and cautery can be a simple and effective treatment with less pain, rapid healing and low recurrence rates. The procedure allows histological evaluation of the specimen but invasive SCC cannot always be excluded. Therefore, it is recommended that clinically suspicious lesions should be fully excised with a small diagnostic margin (2 mm).

KEY POINTS

- Most premalignant lesions are induced by ultraviolet light.
- They can transform to skin cancer, mainly SCC.
- The only intervention that will reduce the formation of AKs is photoprotection.
- It is important to teach patients how to detect skin cancer.

NON-MELANOMA SKIN CANCERS

BCC and SCC are the two most important types of NMSC. BCC is the commonest cancer worldwide and constitutes nearly 75% of all NMSCs, followed by SCCs. These cancers commonly affect white skinned individuals and are very rare in darker and Afro-Caribbean skin.

Risk factors

Several host, environmental and genetic factors are implicated in the pathogenesis of NMSCs. Middle- or old-aged, fair skinned individuals with Fitzpatrick skin type I or II are at increased risk. The frequency of these cancers increases significantly with immunosuppression. Chronic exposure to sunlight, especially since childhood, is associated with an increased risk for SCCs while intermittent and intense exposures are thought to be more relevant for the development of BCCs. The risk is also potentiated by therapeutic use of artificial ultraviolet (UV) light, ionizing radiation and excessive use of recreational tanning beds. SCCs have been known to sometimes develop in non-healing wounds or from chronic irritation. Certain genetic syndromes, such as xeroderma pigmentosum, albinism and epidermolysis bullosa, predispose to all types of NMSCs, and Gorlin's syndrome is a hereditary disorder characterized by multiple BCCs throughout life.

Staging

In the new AJCC 8th edition classification, the entity of non-melanoma skin cancer (cutaneous squamous cell carcinomas and other cutaneous carcinomas) has been eliminated and amalgamated with cutaneous squamous cell carcinoma of the head and neck (**Table 94.1**).[18]

Prevention of NMSCs

The most effective measure for prevention of skin cancers is avoidance of sun exposure. Patients should be advised to avoid deliberate suntanning or using artificial sunbeds. Sunlight should be avoiding during peak daylight hours by wearing appropriate clothing in the form of long-sleeved shirts, wide-brimmed hats and sunglasses.[19] Sunblock with broad spectrum UVA and UVB protection can offer further protection. Those who have precursor lesions (i.e. actinic keratoses and BD) should be educated about the recognition of skin cancer and advised to seek medical attention early.

Basal cell carcinoma

Basal cell cancer (BCC) is the commonest type of skin cancer and arises from the basal keratinocytes. It is locally invasive and distant metastases are exceedingly rare.

CLINICAL FEATURES

BCCs are slow growing tumours and develop for months or years. They are commonly found on the head and neck and may grow to a large size. They may invade deeper structures such as cartilage, muscle or bone. There are several types of BCC that have different clinical appearances. The commonest form is the nodular BCC; it appears as a raised lesion with a rolled edge, telangiectasia and central ulceration – constituting the features of the classical 'rodent ulcer' (**Figure 94.2**). Another variant

TABLE 94.1 TNM staging for Cutaneous SCC of the Head and Neck. Adapted from AJCC Cancer Staging Manual 8th Edition. MB Amin ed. Springer 2017[18]

T: Primary tumour		
Tx	Primary tumour cannot be identified	
Tis	Carcinoma in situ	
T1	Tumour <2 cm in greatest diameter	
T2	Tumour 2–4 cm in greatest diameter	
T3	Tumour >4 cm in greatest diameter or Minor bone erosion or Perineural invasion or Deep invasion (beyond subcutaneous fat or >6 mm thickness	
T4		
T4a	Gross cortical bone/marrow	
T4b	Skull base invasion and/or skull base foramen invasion	
N: Regional Lymph nodes	Clinical (cN)	Pathological (pN)
Nx	Regional lymph nodes cannot be assessed	
No	No Regional lymph node metastasis	
N1	1 ipsilateral lymph node, <3 cm, ENE (-)	
N2		
N2a	1 ipsilateral lymph node, 3–6 cm, ENE (-)	1 single lymph node (ipsi lateral or contralateral), <3 cm, ENE (+) 1 ipsilateral lymph node, 3–6 cm ENE (-)
N2b	Multiple ipsilateral lymph nodes, <6 cm, ENE (-)	
N2c	Bilateral or contralateral lymph nodes, <6 cm, ENE (-)	
N3		
N3a	Any lymph node >6 cm, ENE (-)	
N3b	Any lymph node ENE (+)	1 single ipsilateral lymph node >3 cm ENE (+) or Multip;e ipsilateral, contralateral or bilateral lymph nodes, any with ENE (+)
M: Distant metastasis		
M0	No distant metastasis	
M1	Distant metastasis	
Stage		
0	Tis N0 M0	
1	T1 N0 M0	
2	T2 N0 M0	
3	T3 N0 M0	
	T1-3 N1 M0	
4	T1-3 N2 M0	
	T4 N0-3 M0	
	T1-4 N3 M0	
	T1-4 N0-3 M1	

ENE, Extranodal extension.

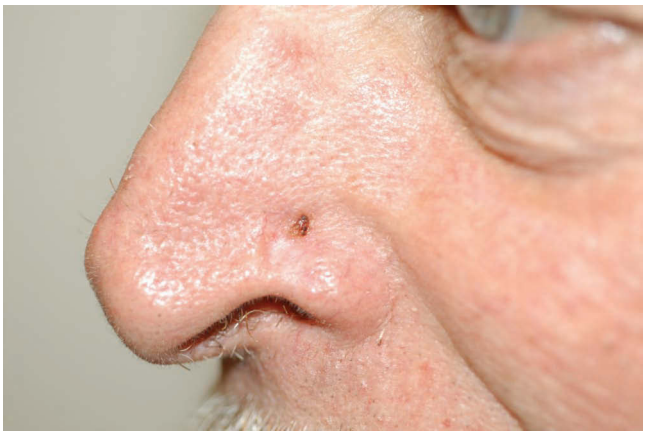

Figure 94.2 Basal cell carcinoma.

is the superficial BCC, which presents as a macule or thin plaque and can be difficult to distinguish from AKs or BD. The morphoeic or infiltrative varietes presents as a poorly demarcated, atrophic and scar-like lesion that, on microscopic examination, shows extensive invasion beyond its perceived boundaries. Cystic, micronodular and pigmented types of BCCs also exist.

DIAGNOSIS

The differential diagnosis includes a range of benign conditions such as seborrhoeic keratosis, sebaceous hyperplasia, trichoepithelioma, lichenoid keratosis, BD or intradermal naevus, but also malignancies such as SCC, sebaceous carcinoma (SC) or melanoma. The diagnosis is confirmed on histological examination. Due to their slow growing nature, it is acceptable to perform a small punch biopsy for confirmation before fully excising the lesion. Histology shows islands of basaloid cells in the dermis with peripheral palisading, and clefting or retraction artefact surrounding the tumour. Perineural invasion, if present, signifies higher chances of recurrence following surgery. Imaging techniques such as computerized tomography or magnetic resonance imaging may be employed to assess invasion of bone, nerves, orbit or parotid gland.

MANAGEMENT

There are several guidelines for the management of BCCs.[20, 21] They all discuss the treatments outlined below.

Non-surgical treatments

Superficial BCC (sBCC) can be treated without surgery using imiquimod cream, PDT or cryotherapy. Imiquimod can achieve cure rates of more than 80% with a regimen consisting of once daily treatment five times a week for 6 weeks.[22] A local inflammatory reaction consisting of erythema, erosion and scabbing is expected and the severity correlates with higher success rates. PDT can also

achieve high rates of clearance and can vary depending on the photosensitizer from 75% to 95%.[23,24]

Surgical treatment

Nodular and morphoeic BCCs are best treated with surgical excision. Small, well-defined lesions may be excised with peripheral margins of 4–5 mm and deep margins down to fat. This method has a clearance rate of approximately 95%. The adequacy of excision is judged by histological clearance of at least 1 mm at both the peripheral and deep margins. Infiltrative, morpheic or large BCCs will need wider margins to achieve the same success rate.

High-risk lesions are defined as those that are poorly defined, larger than 2 cm, located on the central face or histologically shown to be morphoeic or infiltrative. High-risk lesions should be considered for Mohs micrographic surgery, a highly effective and cost-effective technique that allows the assessment of 100% of the margin under frozen sections (**Figure 94.3**). Once adequate clearance of the tumour is achieved the defect is closed using reconstructive surgery. This technique offers very high cure rates reported to be between 98% and 100%.[25,26]

Radiotherapy

BCCs are highly radiosensitive, with cure rates ranging from 79% to 100%.[27] Radiotherapy can be offered as a stand-alone alternative to surgery or as adjuvant treatment for incompletely excised tumours. It is contraindicated for recurrent tumours in previously irradiated areas. It is usually reserved for elderly patients. The treatment is offered in fractions requiring several hospital visits but in the very elderly a single fraction may suffice. The use of weekly dosing for this age group has also been reported.[28]

Treatment for advanced disease

For locally advanced BCCs not suitable for the above approaches, electrochemotherapy can be used.[29] Vismodegib, a hedgehog inhibitor, can also be used[30] for locally advanced or metastatic disease.

FOLLOW-UP

Completely excised BCCs do not require regular follow-up. For marginally excised lesions a decision to review over a 12-month period may be made to look for recurrence.

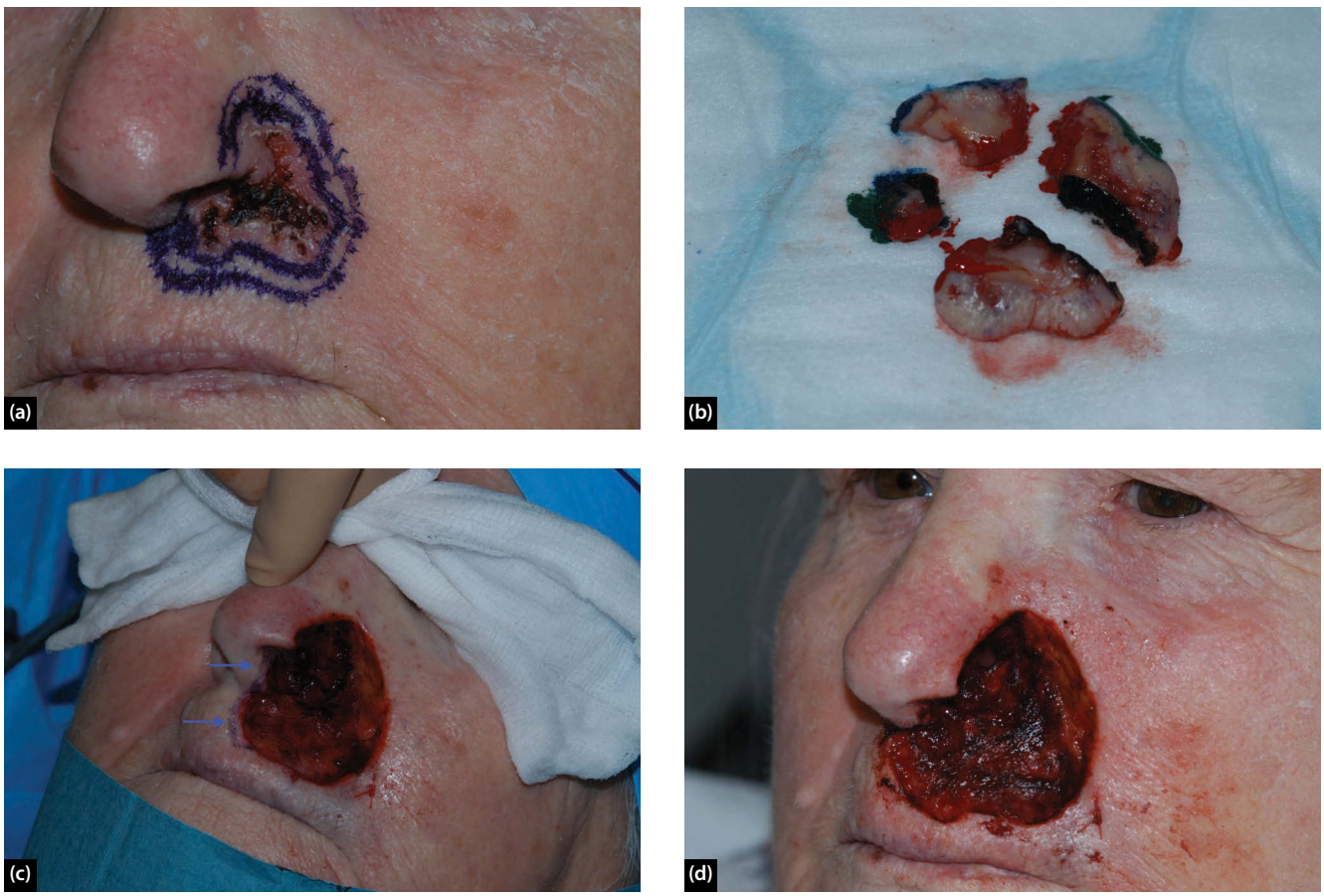

Figure 94.3 Mohs micrographic surgery. **(a)** BCC affecting lip, nose and cheek, marked for surgery. **(b)** After initial debulking, the lesion is removed, separated in blocks and color coded ready for processing in the cryostat. **(c)** After identifying an incompletely excised area in the lip and columnella, a second stage is marked (blue arrows). **(d)** Surgical defect after the second stage. This was clear and is now ready for reconstruction.

KEY POINTS

- BCC is the most common cancer in the world.
- Its incidence is continuing to rise.
- Topical treatments may be sufficient for low-risk BCC.
- For high-risk BCC, the gold standard is Mohs micrographic surgery.
- For advanced disease, radiotherapy, electrochemotherapy and vismodegib can be used.

Squamous cell carcinoma

SCC is the second most common NMSC. It is a malignant neoplasm of the keratinocytes that may arise *de novo* or from precursor lesions (i.e. AKs and BD). SCCs have the potential to metastasize. This risk is generally low (< 5%), but when it happens, the 5-year survival rates are 25–40%.[31] There is a group of SCCs that have a higher risk of developing metastasis. This includes locally advanced disease, poorly differentiated or undifferentiated histology, high-risk areas and immunosupression.

CLINICAL FEATURES

SCCs are found on sun-exposed areas of skin, commonly arising on the face, scalp, ears, lip, hands and forearms but may arise from mucous membranes. The surrounding skin usually shows evidence of chronic actinic damage. They usually grow quickly over weeks or months. Lesions may appear as enlarging plaques, papules or nodules that may be smooth and soft or rough and hardened (**Figure 94.4**). The edges are usually irregular and the base is indurated. With progression they can ulcerate and bleed and may become painful. On the mucosal surfaces they may present as thickened white plaques (leukoplakia) or moist erythematous plaques.

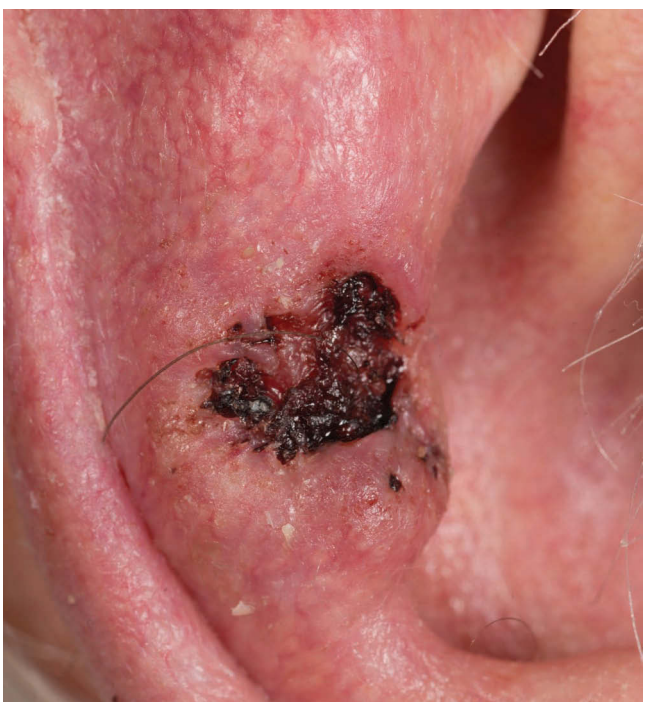

Figure 94.4 Squamous cell carcinoma.

Occasionally SCCs appear as non-healing ulcers with no evidence of keratinization. When they metastasize it is usually to the regional lymph nodes. If distant metastatic disease happens, the most common site is the lungs.

DIAGNOSIS

The differential diagnosis includes other malignant lesions (amelanotic melanoma, BCC, SC) or benign lesions (hypertrophic BD or AK, viral warts, pyogenic granuloma, keratoacanthoma). Histological confirmation is essential for diagnosis. When clinical uncertainty exists, a punch or incisional biopsy may be obtained before excision of the lesion. When doing a biopsy it is important to bear in mind the risk of sampling error, more so when assessing lesions that arise from a very photodamaged skin. In those cases, diagnosic excision may be necessary. The microscopic features include proliferation of atypical keratinocytes, nuclear pleomorphism, keratin whorls and mitotic figures. The degree of these changes may vary. The depth of invasion, histological grade and extension around nerves correlate well with prognosis. When lymph node metastasis is suspected a fine-needle aspiration (FNA) may be performed for cytological analysis. If FNA is inconclusive a radiologically guided core biopsy may be obtained.

MANAGEMENT[32–34]

Surgical treatment

The treatment of choice for most SCCs is surgical excision. It allows examination of the tumour in its entirety and assessment of adequacy of treatment. Well-defined T1 lesions should be excised with a peripheral margin of at least 4 mm and down to the subcutaneous fascia. T2 should be excised with a margin of 6 mm or more.

SCCs with high-risk features may be excised using Mohs micrographic surgery, which has been reported to provide high cure rates.[35] This technique is particularly useful for areas where wider margins of excision may be technically difficult or cause significant visual and functional impairment or if there is nerve involvement.

Radiotherapy

Radiotherapy can be used as a primary treatment for selected patients or adjunct when there is incomplete surgical excision or perineural invasion. The main disadvantages are lack of histological control, secondary skin cancer and atrophy and telangiectasia in the long run. Sites that respond well to radiotherapy include lower eyelid, inner canthus, tip of nose and lip. Radiotherapy should be avoided in tumours that invade bone or cartilage due to the risk of radionecrosis.

KEY POINTS

- SCC is the second most common cancer.
- It has a low but real risk of metastasis.
- No imaging is required in Stage I disease.
- Surgery should be carried out with 4 mm margins for low risk and 6 mm for high risk.
- Radiotherapy is a very effective treatment modality.

MELANOMA

Melanoma is a malignant neoplasm of melanocytes. It accounts for 5% of all skin cancers but 75% of all skin cancer-related deaths, due to its metastatic potential.

Epidemiology

Melanoma can occur in any ethnic group but is much more common in white skinned populations. The highest incidence rates are reported in Australia and New Zealand with 40–60 per 100 000 individuals affected each year.[36] In the US it is estimated to affect 18 per 100 000 and in Europe 10 to 15 patients per 100 000 yearly. These figures appear to be rising worldwide. It can affect any age but the median age at diagnosis is 59 years. Melanoma affects males and females equally.

Risk factors

SKIN TYPE

Fair skinned people are at greater risk of developing melanoma. Having a tendency to burn easily and tan poorly, blonde hair and freckles doubles an individual's risk.[37] Melanoma rarely presents in non-white people, who are 10–20 times less likely to develop this skin cancer.

SUN AND ULTRAVIOLET LIGHT EXPOSURE

Intermittent and intense exposure to sunlight can increase the chances of developing melanoma. Sunburn during childhood is thought to be a risk factor. Studies also support the association of sunbed use with melanoma, especially in those who start to use them before 35 years of age.[38] However, this malignancy can be seen on sites not routinely exposed to sunlight, such as the sole of the foot, genitalia and mucosal surfaces.

FAMILY HISTORY

Patients with an affected first-degree relative are twice as likely to develop melanoma.[39] Germline mutations in the *CDKN2A* gene are found in some families. Inherited photosensitivity disorders such as xeroderma pigmentosum are associated with a high incidence of melanoma and NMSC.

MULTIPLE NAEVI

The risk of melanoma is increased in individuals with a large number of moles. According to a meta-analysis, those with >100 naevi are seven times more likely to develop melanoma compared to mole counts of <15.[40] The presence of multiple clinically atypical naevi also increases the risk significantly. Studies indicate a sixfold increase in people with more than five atypical naevi compared to those with none.

Clinical features

Malignant melanocytic cells can initially appear in the epidermis. This is termed melanoma *in situ*. As it is only in the epidermis, it is not considered to have metastatic potential (**Figure 94.5**).

The four main clinical and pathological subtypes of invasive melanoma are superficial spreading melanoma (SSM), nodular melanoma (NM), lentigo maligna melanoma (LMM) and acral lentiginous melanoma (ALM). Rarer types include mucosal and desmoplastic melanoma and occasionally metastatic melanoma is diagnosed with no known primary.

SUPERFICIAL SPREADING MELANOMA

SSM is the commonest type of melanoma. It presents initially as a flat lesion that undergoes change in size, shape or colour (**Figure 94.6**). Histologically a radial or horizontal growth phase is apparent in the early stages but over time nodular areas with vertical growth may appear.

NODULAR MELANOMA

NM presents as a raised, firm lesion, which may erode or bleed. This type is commonly found on the head and neck and presents more often in older individuals. Lesions may be uniformly coloured or even non-pigmented. Histologically there is a prominent vertical growth phase without radial growth.

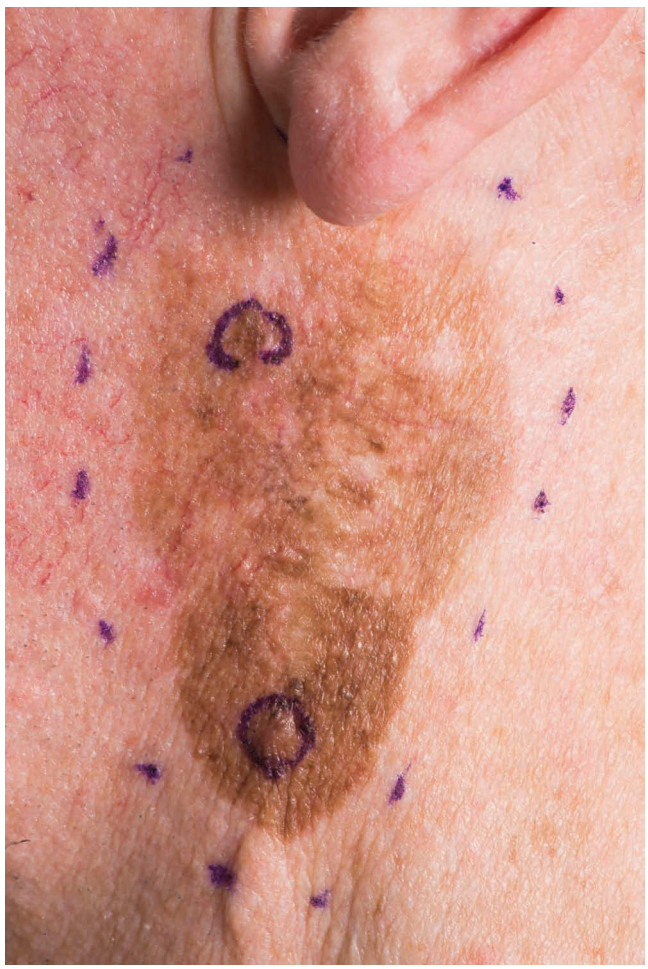

Figure 94.5 Lentigo maligna / melanoma *in situ*.

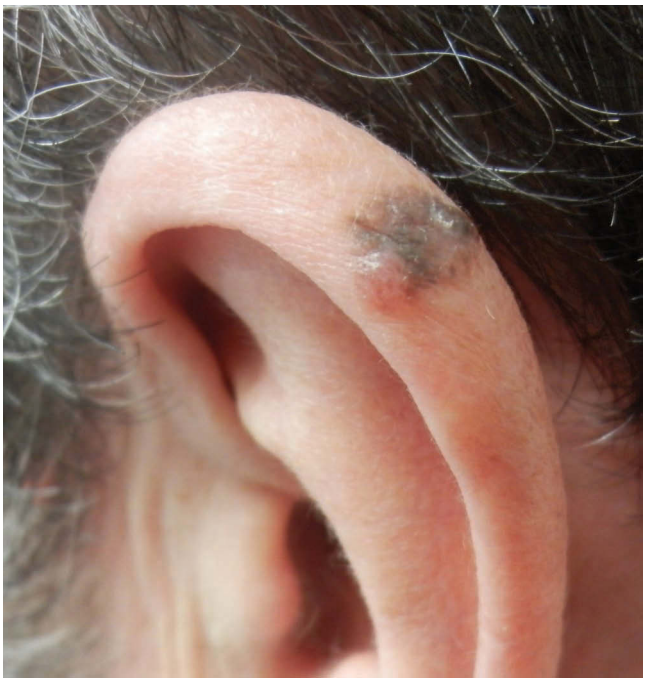

Figure 94.6 Melanoma.

TABLE 94.2 TNM staging for Mucosal melanoma of the Head and Neck. Adapted from AJCC Cancer Staging Manual 8th Edition. MB Amin ed. Springer 2017[18]

T: Primary tumour	
T3	Tumour limited to mucosa and underlying soft tissue regardless of thickness or dimension
T4	
T4a	Moderately advanced disease
T4b	Very advanced disease: Invasion of brain, dura, skull base, lower cranial nerves, masticator space, carotid artery, prevertebral space, or mediastinal structures
N: Regional Lymph nodes	
Nx	Regional lymph nodes cannot be assessed
N0	No Regional lymph node metastasis
N1	
M: Distant metastasis	
M0	No distant metastasis
M1	Distant metastasis

LENTIGO MALIGNA MELANOMA

LMM arises from a precursor lesion called lentigo maligna, which is a slowly growing dark patch on sun-exposed skin. It has a strong predilection for the head and neck of elderly patients. Histologically LMM is characterized by lentiginous proliferation of atypical melanocytes at the dermo-epidermal junction and background changes of chronic sun damage.

ACRAL LENTIGINOUS MELANOMA

ALM arises on the palms and soles or in the nail bed. The incidence is equal in fair and dark-skinned individuals and may not be related to ultraviolet light exposure. It appears as a flat lesion, which may be light coloured or pink. Histology in the early phase may show horizontal or intraepidermal growth but later nodular growth with invasion is seen.

OTHER TYPES OF MELANOMA

Primary melanoma arising from mucosal surfaces is rare. It may present in the oral cavity, nose or sinuses and may metastasize to lymph nodes or distant sites. The prognosis of mucosal melanoma is poor, with 5-year survival rates reported to be 38% according to a recent study.[41] Because of this, the AJCC in its 8th ed is current separated head and neck mucosal melanoma from cutaneous melanoma (**Table 94.2**).

Desmoplastic melanoma is another uncommon type typically found on the head and neck. Affected individuals are older and have chronically sun-damaged skin. The appearance of the lesion may be non-specific and it may look similar to a keloid scar or a benign lesion called dermatofibroma. Histologically an abundance of collagen is found and there may be prominent neural involvement. The 5-year survival rate is around 85%.[42]

Although most melanomas present as cutaneous lesions, occasionally metastatic deposits are found without any signs of a primary tumour. The original lesion may be hidden or may have undergone complete regression due to lymphocyte activation by the immune system. In such cases a careful search for a hidden primary should be performed by doing a full skin examination. They should also have an eye examination (looking for ocular melanoma), ENT and colonoscopy. In some cases, full PET-scanning is used.

Prognostic factors

The most important prognostic factor for patients with melanoma is the clinical stage. For localized melanoma the following characteristics of the tumour are considered to be the key determinants of outcome:

- **Breslow thickness:** this is the microscopic measurement of vertical depth of the tumour and is expressed in millimetres. It has shown to be one of the most important predictors of risk in a large study of 17 600 patients.[43]
- **Ulceration:** the histological presence of ulceration is another important factor that affects the prognosis of melanoma. The survival rate for ulcerated melanomas has been shown to be equivalent to that of non-ulcerated melanomas of the next greatest thickness category.
- **Mitotic rate:** high mitotic activity in the tumour is an independent risk factor that denotes biological aggressiveness of a melanoma.[44, 45]

Other factors that have been reported but are thought to be less relevant are anatomic location, patient age, gender,

level of tissue invasion (Clarke level), histological regression, lymphocytic infiltration and vascular invasion.

Staging

The American Joint Committee on Cancer published a revised staging system of melanoma in 2016, which is widely accepted as standard. In this classification, melanoma has been split into head and neck mucosal melanoma (**Table 94.2**), cutaneous melanoma (**Table 94.3**), conjunctival melanoma and uveal melanoma. When stratified by stage, the 5-year survival curves of melanoma goes from 97% for stage IA to 15% for stage IV (**Table 94.4**).

Management

ROLE OF SKIN SPECIALIST MULTIDISCIPLNARY TEAM

Melanomas above a certain Breslow thickness should be managed in the context of a multidisciplinary team (MDT). The team should ideally include histopathologists, radiologists, oncologists, dermatologists, plastic surgeons and other surgical specialties such as ENT or maxillo-facial surgeons. It is important to recognize the role of specialist cancer nurses in these meetings as they commonly have a very good knowledge of the patient's psychosocial needs. This MDT should consider on an individual basis the appropriate treatment, the role of sentinel lymph node biopsy (SLNB), adjuvant radiotherapy and inclusion in clinical trials.

SURGERY

Treatment of primary melanoma is surgical removal. Initially all suspected melanomas should be excised down to fat with a 2 mm margin to establish the Breslow thickness. Partial thickness, punch or incisional biopsies should not be performed as they may lead to diagnostic uncertainty. Once the thickness is established, a wider and deeper excision is performed. Margin recommendation varies slightly in different countries (**Table 94.5**).[46–50] The National Institute for Health and Care Excellence (NICE) recommends at least 5 mm margins for stage 0 melanomas, at least 10 mm for stage 1 and at least 20 mm for stage 2.[51]

Mohs micrographic surgery can be used to treat lentigo maligna (*in situ* melanoma), invasive lesions with indistinct margins such as desmoplastic melanoma or for surgery close to important anatomical areas such as eyes or ears. Clinical data for this technique in the management of melanoma are limited,[52] however, and should only be used under the auspices of an MDT.

INVESTIGATIONS

Investigations for stage I and IIA and B melanoma are not required. Patients with stage IIC or above should have a CT scan of the head, chest, abdomen and pelvis. For those with stage IV disease, serum lactate dehydrogenase (LDH) should also be measured. Full body PET-CT can also be used. However, due to the rapid development of new, more effective treatments, this recommendation is likely to change in the future.

TABLE 94.3 TNM staging for cutaneous melanoma. Adapted from AJCC Cancer Staging Manual 8th Edition. MB Amin ed. Springer 2017[18]

T: Primary tumour	
Tx	Primary tumour thickness cannot be assessed
T0	No evidence of primary tumour
Tis	Melanoma in situ
T1	
T1a	Breslow <0.8mm thick without ulceration
T1b	Breslow <0.8mm thick with ulceration
	Breslow 0.8 - 1mm thick without ulceration
T2	
T2a	Breslow 1.1-2mm thick without ulceration
T2b	Breslow 1.1-2mm thick with ulceration
T3	
T3a	Breslow 2.1-4mm thick without ulceration
T3b	Breslow 2.1-4mm thick with ulceration
T4	
T4a	Breslow >4mm thick without ulceration
T4b	Breslow >4mm thick with ulceration
N: Regional Lymph nodes	
Nx	Regional lymph nodes not assessed
N0	No Regional lymph node metastasis
N1	
N1a	1 clinically occult lymph node (i.e. SLNB)
N1b	1 clinically detected lymph node
N1c	No lymph nodes, presence of in-transit, satellite or microsatellite metastasis
N2	
N2a	2-3 clinically occult lymph nodes
N2b	2-3 lymph nodes, at least 1 clinically detected
N2c	1 lymph node with presence of in-transit, satellite or microsatellite metastasis
N3	
N3a	>4 clinically occult lymph nodes
N3b	>4 lymph nodes, at least 1 clinically detected
N3c	>2 lymph node with presence of in-transit, satellite or microsatellite metastasis Matted lymph node metastasis
M: Distant metastasis *	
M0	No distant metastasis
M1	
M1a	Distant metastasis to skin, soft tissue or non-regional lymph nodes
M1b	Lung metastasis with or without M1a
M1c	Distant metastasis to non-CNS visceral sites, with or without M1a or M1b
M1d	CNS metastasis with or without M1a M1b or M1c
Stage	
0	Tis N0 M0
IA	T1a N0 M0

(Continued)

TABLE 94.3 *(Continued)* TNM staging for cutaneous melanoma. Adapted from AJCC Cancer Staging Manual 8th Edition. MB Amin ed. Springer 2017[18]

IB	T1b N0 M0 T2a N0 M0
IIA	T2b N0 M0 T3a N0 M0
IIB	T3b N0 M0 T4a N0 M0
IIC	T4b N0 M0
IIIA	T1a/b, T2a N1a or N2a M0
IIIB	T0 N1b, N1c Mo T1a/b, T2a N1b/c, N2b M0 T2b, T3a NN1a-N2b M0
IIIC	T0 N2b, N2c, N3b, N3c M0 T1a-T3 N2c,N3a/b/c M0 T3b/T4a any N>=N1 M0 T4b N1c-N2c M0
IIID	T4b N3a/b/c M0
IV	Any T any N M1

*Suffixes in all M categories: (0) LDH not elevated; (1) LDH elevated.

TABLE 94.4 Survival rates for cutaneous melanoma

Stage	5-year survival (%)	10-year survival (%)
Stage IA	97	95
Stage IB	92	86
Stage IIA	81	67
Stage IIB	70	57
Stage IIC	53	40
Stage IIIA	78	68
Stage IIIB	59	43
Stage IIIC	40	24
Stage IV:	15–20	10–15

LYMPH NODE DISEASE

For patients with no apparent lymph node involvement, a SLNB may be performed at the time of wider excision. The sentinel lymph node is the first node where the skin involved with melanoma drains to and is detected by injecting a blue dye that is visually traced and by detecting the path of a radioactive tracer. SLNB is offered for stage 1B disease or above. The procedure has prognostic significance[53] but to date there has been no proven impact in melanoma-specific survival.[54]

For clinically enlarged nodes a FNAC sample should be obtained. If negative or equivocal this may be repeated, or an image-guided core biopsy or open biopsy should be performed.

If a lymph node is involved, then completion lymphadenectomy should be performed. For head and neck, it should include levels 1–5. Superficial parotidectomy can be performed if the disease is in that area. Radical parotidectomy is usually saved for cases of parotid involvement.

Adjuvant radiotherapy can be used to a lymph node basin. There is evidence that in high-risk patients, it reduces local recurrence, without an improvement in overall survival.[55]

LOCOREGIONAL METASTASES

Metastatic disease confined to the skin between the scar of the primary lesion and regional lymph node basins may be treated palliatively by surgical excision or ablative techniques such as CO2 laser or electro cautery. Radiotherapy may be used if these fail. Electrochemotherapy using intravenous bleomycin is an emerging palliative modality for locoregional metastatic melanoma.[56] Interleukin-2 is licensed in the United States, but there is limited data. Interferon alpha may have a benefit in high-risk melanomas (stage II–III) in disease-free survival and, perhaps, in overall survival, although trials are still ongoing.[57]

DISTANT METASTASES

Patients with stage IV disease should be referred to an oncologist. Palliative surgery or radiotherapy may be offered for oligometastaic disease. Historically chemotherapeutic options have been limited to dacarbazine, which has limited benefit with response rates ranging from 5% to 28%. In recent years, due to the discovery of signalling pathways and mutations in those pathways, new targeted therapies have emerged. For BRAF mutations, vemurafenib and dabrafenib are available, often used along MEK inhibitors such as trametinib. Of special interest in head and neck is a mutation in KIT that is present in 39% of cases, and for which imatinib is available (but unlicensed for this indication). There is also the developing of immunotherapies such as ipilimumab (anti-CTLA-4); pembrolizumab

TABLE 94.5 Melanoma surgical margins recommended by different guidelines

Thickness (mm)	UK (cm)	German (cm)	European (cm)	American (cm)	Australia / New Zealand (cm)
In situ	0.5	0.5	0.5	0.5	0.5
<1	1	1	1	1	1
1–2	1-2	1	1	1–2	1–2
2–4	2–3	2	2	2	1–2
>4	3	2	2	2	2

TABLE 94.6 Melanoma follow-up (taken from the British Association of Dermatologists melanoma guidelines)

Stage IA	3 to 6 monthly for 12 months
Stage IB to IIIA	3 monthly for 3 years, then
	6 monthly to 5 years
Stage IIIB and IIIC	3 monthly for 3 years, then
	6 monthly to 5 years, then
	Annually to 10 years
Stage IV	See according to need

and nivolumab (anti-PD1). With multiple molecules being developed currently, the next few years are likely to completely rewrite the way we approach and treat melanoma.

Follow-up

Patients with *in-situ* melanoma do not require follow-up. Patients with stage I and above disease require monitoring on a regular basis for assessment of recurrence or metastatic spread. Guidelines on the timings vary but the schedule based on the British Association of Dermatologists recommendations can be used as a guide (**Table 94.6**).

KEY POINTS

- Melanoma accounts for 75% of all skin cancer deaths.
- Its incidence is rising worldwide.
- Mucosal melanoma of the head and neck has a worse prognosis and its own TNM classification..
- The only treatment for primary melanoma is surgery with adequate margins.
- Surgery is the treatment of choice for lymph node metastasis. Levels 1–5 should all be removed.
- Radiotherapy has a role as adjuvant therapy.
- For metastatic disease, it is essential to know the mutation status (BRAF) in order to tailor treatment.

RARE SKIN CANCERS

Merkel cell carcinoma

Merkel cell carcinoma (MCC) is an uncommon malignancy of neuro-endocrine origin and it is though to be associated to a poliomavirus (MCPyV) in 80% of the cases.[58] However, its incidence has increased fourfold since 1986.[59] It is usually seen in elderly, white-skinned individuals but may arise in younger adults, particularly those who are immunosuppressed. The incidence is highest on the head and neck (40–60%).[60] The morphology of skin lesions is variable and it may mimic a number of benign or malignant tumours. A common presentation is an enlarging solid nodule and rapid growth is characteristic (**Figure 94.7**). Due to its increasing incidence and aggressive nature, it has a separate TNM staging in the AJCC classification.

The survival rate depends on the stage at diagnosis (**Table 94.7**).[61]

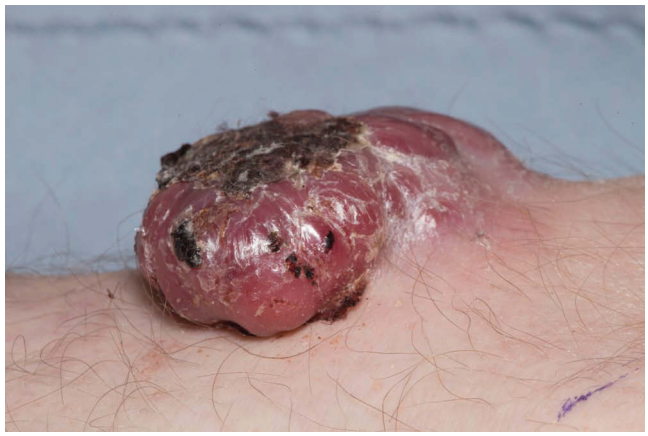

Figure 94.7 Merkel cell carcinoma.

TABLE 94.7 5-year survival rates for Merkel cell carcinoma. Adapted from AJCC Cancer Staging Manual 8th Edition. MB Amin ed. Springer 2017[18]

AJCC clinical staging	
I	55.8%
IIA	41.1%
IIB	31.8%
III	35.4%
IV	13.5%

Traditionally MCC has been treated with surgery with wide margins (up to 3 cm). However, MCC is radiosensitive and radiotherapy can be used as first line or as adjuvant to surgery. Current trials are trying to ascertain the efficacy of these treatment modalities.

Dermatofibrosarcoma protuberans

Dermatofibrosarcoma protuberans (DFSP) is the commonest sarcoma of the skin with 14% of DFSPs arising in the head and neck.[62] These tumours exhibit slow growth and are locally infiltrative. They often recur locally following treatment but lymphatic or distant spread is uncommon. They can arise in any age group but the highest incidence is seen in 20–40-year-olds. Lesions appear as plaques or nodules that are fixed to the dermis and the overlying skin may be atrophic or telangiectatic. The treatment is surgical excision with wide margins. Mohs micrographic surgery can offer greater chances of complete removal and is advocated by many as the treatment of choice.[63,64] Other treatment options include radiotherapy and imatinib; these are usually employed for unresectable or metastatic disease. Although with total margin control surgery recurrences are very rare, due to the historical high rates of local recurrences follow-up is normally suggested (6–12 monthly).

Atypical fibroxanthoma

Atypical fibroxanthoma (AFX) is an uncommon spindle cell tumour. Most tumours affect the head and neck and are usually seen in elderly individuals with chronically

sun-damaged skin. The usual clinical presentation is a rapidly growing ulcerated nodule but the appearance may be non-specific and lesions are often confused with BCCs or SCCs. The incidence of metastases is low and most AFXs follow a benign clinical course. The treatment of choice is complete micrographic surgical excision.[65]

Angiosarcoma

Cutaneous angiosarcoma is a rare vascular neoplasm that is most commonly seen in patients over 50 years of age. Up to 60% of these cancers arise in the head and neck. The initial appearance is often a bruise-like plaque that progresses to larger nodules but they can look non-specific, presenting with oedema or ulceration (**Figure 94.8**). They carry a high risk of local recurrence and distant metastases to lymph nodes, lung and liver. The 5-year survival has been estimated in 15%,[66] with size (5 cm cut off) being the main prognostic factor. The ideal treatment has not been established but combined surgery and local radiotherapy appear to have better results than either treatment done alone.[67] Chemotherapeutic agents such as paclitaxel appear to have some benefit and are being evaluated.[68]

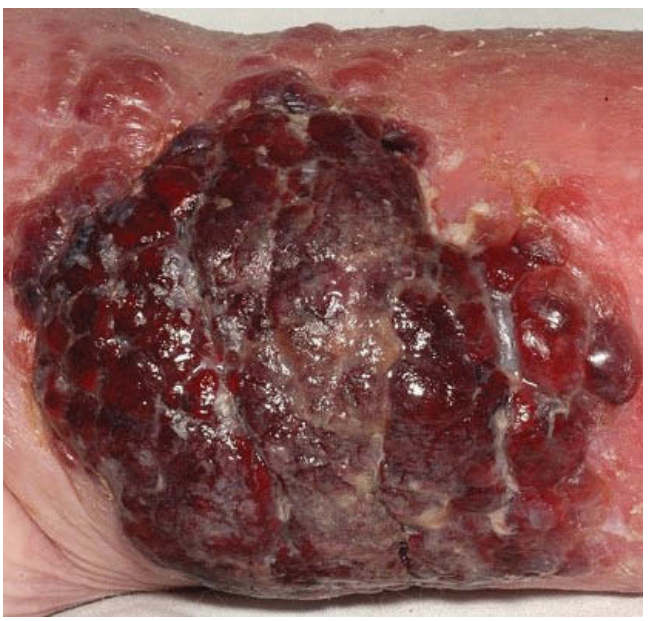

Figure 94.8 Angiosarcoma.

Sebaceous carcinoma

Sebaceous carcinoma (SC) arises from the sebaceous glands. They most commonly affect the head and neck, with the eyelids reported as being the most common site. It is more common in older patients. It has been associated with Muir-Torres syndrome and Lynch syndrome so all patients with SC should be assessed for this.

Its appearance can vary widely, often mimicking other benign and malignant cutaneous lesions. Classically they have a firm yellowish appearance.

The treatment of SC is surgical. With conventional excision with 5–6 mm margins, the recurrence rate is 32%.[69] Because of the high local recurrence rate, Mohs surgery is favoured over conventional excision, with recurrences reported from 0%[70] to 11%.[71] SC has the potential to spread, with a 5-year survival rate of 91%, a 10-year survival rate of 79%[72] and a mortality rate of 5–10%.

Skin cancer in immunosuppressed patients

Immunosuppression from any cause, such as HIV-AIDS, malignancy, chemotherapy and drugs, increases the likelihood of developing skin cancer. Most skin cancers in immunosuppressed patients are SCCs[73] but the incidence of other skin cancers such as BCCs, melanoma, MCC and Kaposi sarcoma is increased several-fold compared to immunocompetent individuals. These patients may develop multiple cutaneous neoplasms over their lifetime and regular surveillance of their skin is recommended.

BENIGN LESIONS

Melanocytic lesions

LENTIGINES

Lentigines (singular lentigo) are benign lesions that appear as small, pigmented flat spots surrounded by normal skin. There are several types and the commonest form is a simple lentigo that is not caused by solar radiation or systemic disease. Solar lentigines are common in fair skinned individuals and the incidence increases with age. They may also result from tanning beds, therapeutic ultraviolet light treatment and radiation. A large number of lentigines are seen in patients with xeroderma pigmentosum. Lentigines can appear on the lips, gums or oral mucosae and may be associated with organ abnormalities such as in Peutz-Jeghers syndrome.

MUCOSAL MELANOCYTIC LESIONS

Diffuse oral mucosal melanosis is often physiological in dark skinned individuals but may arise as a result of smoking, medication or following inflammation. The differential diagnosis of focal melanotic lesions includes benign melanotic macules, melano-acanthoma, melanocytic naevi and melanoma. Benign melanotic macules are synonymous with lentigines and are described above. A melano-acanthoma is a benign lesion that often rapidly increases in size and usually resolves without treatment or following biopsy. Melanocytic naevi in the oral cavity are usually acquired rather than congenital and have a smooth surface. They do not transform to melanoma but a biopsy should be performed for new lesions. Mucosal melanoma is rare and can arise in the nose, sinuses or mouth. Within the mouth the palate is the commonest site of involvement and thus all pigmented lesions in this area should be regarded with suspicion.

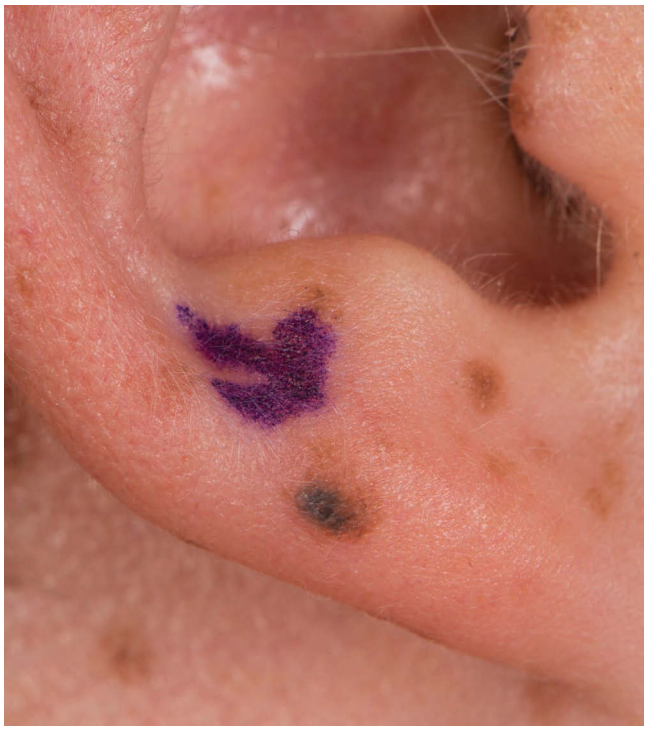

Figure 94.9 Junctional naevus.

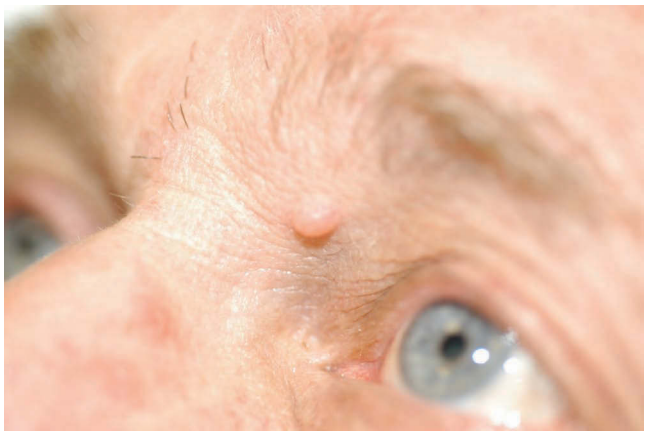

Figure 94.10 Intradermal naevus.

MELANOCYTIC NAEVI

These are benign proliferations of melanocytes that may be congenital or acquired. They may be seen on any part of the skin and are often found on the scalp in children and adults. The incidence of new acquired naevi (**Figure 94.9**) decreases with age. There are three histological subtypes, which can be differentiated clinically. Junctional naevi consist of melanocytic nests at the basement membrane and appear flat macroscopically. When these nests are in the dermis the lesion appears above the surface giving intradermal naevi a papular appearance. Compound naevi have junctional and intradermal components and thus have flat and raised areas on gross examination (**Figure 94.10**). Melanocytic naevi are usually asymptomatic and often come to attention when they become inflamed or irritated, resulting in itching or pain.

ATYPICAL/DYSPLASTIC NAEVI

Atypical nevi are acquired moles with unusual features that may mimic melanoma. Clinically they are often larger than 5 mm in diameter, have irregular borders and may display several shades of pigment. Histology shows foci of atypical melanocytes but no invasion. Several dysplastic naevi may be seen in the same individual and, when accompanied by large number of benign naevi and a family history of melanoma, form the familial atypical mole and melanoma syndrome.[74] These patients are at high risk of developing melanoma. UV light can promote the development of dysplastic naevi and their transformation to melanoma but these lesions can appear in non-exposed sites. Atypical moles should be referred to dermatologists for assessment with dermoscopy, full skin examination and photographic records, especially if there are multiple unusual lesions. Excision with a 2 mm margin is recommended if the lesions change in appearance or when there is diagnostic uncertainty.

Seborrhoeic keratosis

These are benign epithelial tumours and are extremely common. They may be located anywhere on the skin except mucous membranes, palms and soles. The frequency of these lesions increases with age and elderly patients often have numerous seborrheic keratoses. The lesion is usually well defined and appears stuck on the skin (**Figure 94.11**). The surface is rough, corrugated and warty and the colour may range from that of normal skin to dark brown or black. Early lesions may be flat and can cause diagnostic confusion with melanocytic lesions. Dermoscopy shows horn pseudocysts and pseudofollicular openings.[75] Histological confirmation may be required for lesions lacking typical features. Treatment is not essential but can be carried out for cosmetic or symptomatic reasons as the lesions often become irritated or inflamed. Cryotherapy, shave excision and curettage are some of the commonly used surgical techniques.

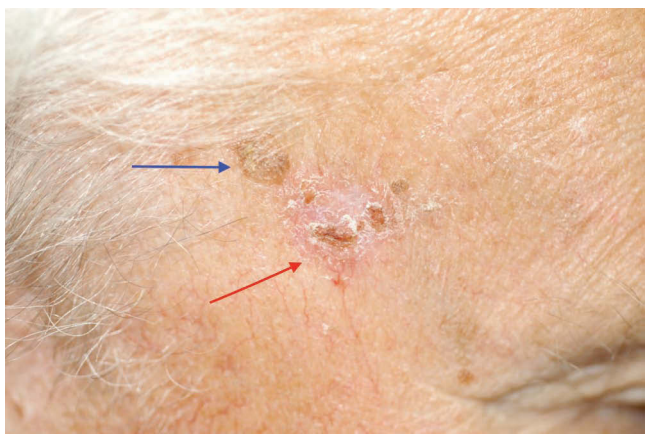

Figure 94.11 Seborrhoeic keratosis (Blue arrow) next to a basal cell carcinoma (red arrow).

Keratoacanthoma

Keratoacanthomas are low-grade squamoproliferative tumours that arise from the pilosebaceous follicles. They grow rapidly and appear as nodules with a central keratin-filled crater and can be difficult to distinguish from SCC clinically. They commonly arise on the head and neck, and intra-oral lesions have also been reported. If untreated the lesions would involute over several months but lesions should be excised for diagnosis and exclusion of SCC.[76]

Cysts

A number of benign cysts can arise on the head and neck. Dermoid cysts are developmental inclusion cysts that appear at birth or in childhood and are commonly seen on the face. They contain mature skin with hair follicles, sweat glands and sebaceous glands. Epidermoid cysts form from proliferation of squamous epithelium in the dermis, which can follow trauma or a blocked pore. They are commonly seen on the face, neck and scalp. Pilar or trichilemmal cysts arise from stratified squamous epithelium similar to that found in hair follicles. Most pilar cysts occur on the scalp but may also form on the face or neck. Cysts may cause problems with cosmesis or symptoms following inflammation, and surgical excision can be offered for these reasons.

Pilomatricoma

A pilomatricoma is a benign tumour that arises from hair matrix cells. It commonly affects children in the form of a solitary, angulated, hard nodule on the cheek, eyelid, scalp or neck. The lesions tend to grow slowly and are usually asymptomatic. Transformation to pilomatrix carcinoma is possible but extremely rare. Multiple lesions may be seen in patients with myotonic dystrophy. These lesions should be excised, as they never regress spontaneously. Recurrence can occur if they are not removed completely.

Sebaceous adenoma

Sebaceous adenomas are benign adnexal neoplasm resulting from the proliferation of sebaceous gland-like structures. They appear as a small, slow growing, smooth, pink or yellow papules with central umbilication on the face or scalp. Lesions may be single or multiple. They may be mistaken for BCCs and histological confirmation is essential. These are rare neoplasms and often linked to Muir-Torre syndrome, which is a hereditary cancer syndrome characterized by visceral malignancies. Sebaceous adenomas should prompt a careful evaluation of the patient with attention to their family history for internal organ cancers.

Sebaceous hyperplasia

This is a common finding in the elderly or those who are receiving long-term immunosuppression. They appear as multiple, skin coloured or yellow papules on the forehead, nose or cheeks that are a few millimetres in diameter. Lesions are often umbilicated and may be confused with BCCs. These lesions have no malignant potential and treatment is not essential but a biopsy may help when the diagnosis is doubtful.

Syringoma

Syringoma is a benign sweat duct tumour. They usually appear in clusters on and around the eyelids or cheeks. Individual lesions are skin coloured papules, 1–3 mm in diameter. Treatment is often sought for cosmetic reasons and options include electrocautery, laser, cryotherapy and trichloracetic acid.

KEY POINTS

- Skin cancers are the most common cancers in the world.
- The incidence of skin cancer is increasing.
- Appropriate management with adequate surgical margins to prevent recurrences is vital.
- Mohs micrographic surgery can offer complete margin control for many skin cancers.
- Rare skin cancers are also on the rise. It is important to recognize them early so that appropriate multidisciplinary approach can be taken.

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CHAPTER 95

FACIAL REANIMATION SURGERY

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SEARCH STRATEGY

Data in this chapter may be updated by a PubMed search using the keywords: facial paralysis, Bell's palsy and facial nerve.

THE CLINICAL PROBLEM

Facial paralysis causes a highly visible deformity with profound consequences from both a functional and psychosocial standpoint.

The absence or dysfunction of facial musculature (**Table 95.1**) can lead to an inability to control the eye and mouth, leading to corneal exposure and chronic irritation of the eye as well as oral incompetence, producing a disfiguring asymmetry and difficulty in eating and drinking.

From a psychosocial viewpoint, the lack of mimetic facial expression produces difficulties in communication and can affect self-confidence, professional advancement and social interaction and produce depression.

Brow ptosis is more commonly a problem in the older patient. The weight of the forehead pushes the eyebrow down, producing eyebrow asymmetry and obstructing upward gaze. This may be complicated by overactivity of the unaffected contralateral frontalis muscle, elevating the contralateral brow, worsening the asymmetry.

The orbicularis oculi muscle is crucial to the protection of the globe, providing closure of the eyelids during blinking, maintaining tone of the lower eyelid and providing the pumping mechanism for the lacrimal drainage apparatus. Paralysis of this muscle prevents eye closure, risking corneal exposure, ulceration and blindness. During normal eye closure, the majority of movement occurs in the upper eyelid – the lower eyelid elevates by approximately 2 mm during forced closure. The absence of Bell's phenomenon (upward rotation of the globe on forced eye closure) is a significant risk factor for the development of corneal exposure and must be assessed.

The normal orbicularis is responsible for the lacrimal pump apparatus. Paralysis of this active pumping mechanism reduces movement of tears down the lacrimal duct into the nasal cavity. Weakness of orbicularis may produce a paralytic ectropion, allowing the lacrimal punctum to fall away from the globe, worsening tear drainage.

The lateral canthus lies 2 mm cranial to the medial canthus; thus, tears naturally flow medially to the punctum and are carried away through the lacrimal apparatus, and are thence actively pumped away by the contractions of orbicularis oculi muscle. Laxity of the lower lid disrupts this smooth gradient, forming a paralytic ectropion, producing a bowing of the lower lid, producing a sump that allows tears to pool, overflow, and then run down the cheek.

As a result, patients with facial paralysis are frequently troubled by dryness of the eye coupled with a watering eye. This is exacerbated during cold and windy weather.

Weakness of the facial muscles may lead to cosmetic and functional problems with the nose. Overactivity of the muscles on the normal side of the face may pull midline structures over to the normal side. The nasal tip is drawn across the midline, along with the philtrum. There may be collapse of the internal and external nasal valves due to paralysis of the dilator nares and levator labii alequae nasi muscles.

TABLE 95.1 Aetiology of facial nerve dysfunction by anatomical level

Intracranial	Intratemporal	Extratemporal

• Vascular abnormalities
• CNS degenerative disease
• Intracranial cavity tumour
• Brain tumour
• Congenital abnormalities and agenesis
	• Bacterial and viral infection
	• Cholesteatoma
	• Trauma:
	  ○ temporal bone fracture
	  ○ gunshot wounds
	• Tumours invading middle ear, mastoid, FN
	• Iatrogenic cause
		• Malignant tumour of parotid
		• Trauma: lacerations, gunshot wounds
		• Iatrogenic
		• Primary tumour of FN
		• Malignant tumour of ascending ramus of mandible, pterygoid and skin

The other major concern for patients is inability to move the mouth. This affects the ability to speak clearly, drink fluids and eat. A common complaint is biting the inside of the mouth when eating. Speech is affected – many facial paralysis patients have difficulty with plosives ('b' and 'p' sounds).

ANATOMY

Facial muscles

There are 17 paired muscles of facial expression and one unpaired sphincter muscle, the orbicularis oris. The major muscles affecting the forehead and eyelids are the frontalis, corrugator and orbicularis oculi. There are two groups of muscles controlling the movement of the lips. The lip retractors include the levator labii superioris, levator anguli oris, zygomaticus major and minor for the upper lip, and depressor labii inferioris and depressor anguli oris for the lower lip. The antagonist to these muscles is the orbicularis oris, which is responsible for oral continence and is also involved in expressive movement of the lips. The detailed anatomy of the facial musculature has been well described in many standard surgical and anatomical textbooks.

Physiology of nerve repair

To understand the strategies employed in the management of facial nerve injury it is important to have an understanding of the principles of nerve repair.

SEDDON'S CLASSIFICATION

Seddon[1] described the following types of neuronal injury:

- **Neuropraxia**. This is temporary cessation of conduction of the nerve with no loss of axon continuity. Neuropraxia is a transient phenomenon with complete recovery once the causative factor is removed.
- **Axonotmesis**. Damage is sustained to the axon resulting in Wallerian degeneration. Regeneration occurs at a rate of 1–4 mm a day and recovery is usually satisfactory.
- **Neurotmesis**. The nerve fibre is severed and the endoneurium disrupted. Recovery is unlikely.[1, 2]

SUNDERLAND'S CLASSIFICATION

Sunderland's classification[3] discusses the extent of nerve injury allowing predictions to be made regarding prognosis:

- **First degree** injury is a conduction delay with no evidence of discontinuity of the neuronal anatomy.
- **Second degree** injury demonstrates disruption to the axon, resulting in Wallerian degeneration of the distal component. The proximal segment of the nerve becomes a passage for proteosynthetic substances to allow axonal regeneration. The endoneurium is intact so the axonal sprout can grow (usually at a rate of 1 mm a day) within the endoneurium, ensuring the motor end plate, and therefore muscles, receive the same nerve supply as prior to the injury. Factors that may affect recovery include site and type of injury, nutritional status and age.[4]
- **Third degree** injury also affects the endoneurium; therefore, in addition to the features seen in type two injury, the neuronal regrowth is less organized as regenerating axons may enter any endoneurial tubules. This means that the subsequent reinnervation may not supply the same muscles as previously, resulting in synkinesis or mass movement.
- **Fourth degree** injury affects the perineurium and **fifth degree** injury affects both perineurium and epineurium. This in turn results in a decreased number of axons regenerating as efficiently as in the less severe injuries, manifesting itself as weaker muscle function and also synkinesis.

The time from axonal degeneration to irretrievable muscle atrophy is accepted to be approximately 18 months but there have been reports of successful reinnervation up to 20 years later.[2]

ASSESSMENT OF THE PATIENT

A detailed clinical assessment is important in the diagnosis of facial paralysis. Attention should be paid to the duration and progression of symptoms, associated history ear problems, trauma, recent vaccinations, travel history, family history of facial weakness and medical history.

A diagnosis of idiopathic Bell's palsy should only be made with a classical history – any atypical clinical features should prompt further investigation to exclude another cause.

Examination should include careful assessment of each branch of the facial nerve and, where possible, the House–Brackmann[5] (**Table 95.2**) and Sunnybrook grading scales[6] should be used to document the severity of facial weakness. The Sunnybrook Facial Grading in particular will allow assessment for recovery or progression (**Table 95.3**). In younger children, where it may not be possible to use the House–Brackmann grading scale, it is important to document what spontaneous facial movements are noted (particularly when the child is crying) and what movement the parents feel may have altered. Forehead sparing in a patient presenting with facial weakness represents a supranuclear lesion due to cross-innervation. A thorough history and examination will reveal the presence of a complete or partial VIIth nerve paralysis and the extent and severity of weakness. The history should explore the physical problems from the patient's perspectives as a guide to treatment. The patient's concerns and expectation should be sought and evaluated: for some, functional considerations will predominate; for others, simply looking symmetrical in photos is all they seek; others will want restoration of dynamic spontaneous facial movement. The level of nerve lesion can be assessed clinically. Injury within the bony canal is suggested by hyperacusis, loss of taste to the ipsilateral tongue and facial weakness. Injury near the geniculate ganglion will result in decreased secretory function of the nose, mouth and lacrimal gland.

TABLE 95.2 The House–Brackman grading scale[5]

Grade	Characteristics
I. Normal	Normal facial function in all areas
II. Mild dysfunction	Gross: • slight weakness noticeable on close inspection • may have slight synkinesis • at rest, normal symmetry and tone Motion: • forehead – moderate-to-good function • eye – complete closure with minimal effort • mouth – slight asymmetry
III. Moderate dysfunction	Gross: • obvious but not disfiguring difference between the two sides • noticeable but not severe synkinesis, contracture, or hemifacial spasm • at rest, normal symmetry and tone Motion: • forehead – slight-to-moderate movement • eye – complete closure with effort • mouth – slightly weak with maximum effort
IV. Moderately severe dysfunction	Gross: • obvious weakness and/or disfiguring asymmetry • at rest, normal symmetry and tone Motion: • forehead – none • eye – incomplete closure • mouth – asymmetric with maximum effort
V. Severe dysfunction	Gross: • only barely perceptible motion • at rest, asymmetry Motion: • forehead – none • eye – incomplete closure • mouth – slight movement
VI. Total paralysis	• No movement

Examination should also include otoscopy, examination of the head and neck for signs of trauma and masses, particularly in the region of the parotid, as well as assessment of the remaining cranial nerves.[3]

Examination of the face begins with the brow. The position of the brow and degree of forehead rhytids must be assessed and brow movement should be measured. The palpebral aperture should then be measured. Visual acuity and the presence of Bell's phenomenon should be tested. Lower lid laxity can be assessed by the snap test, gently pulling the lower lid away from the globe and releasing – adequate tone is demonstrated by a slightly audible snap as the lid is snaps back into position. This fails to occur if lid laxity is present. Alternatively, distraction greater than 6 mm from the globe on gentle downward traction of the lower lid suggests lid laxity is present. The position of the inferior canalicular punctum should be noted and the presence of medial canthal tendon laxity assessed.

The nose is examined for deviation to the unaffected side. Forced inspiration may produce collapse of the internal nasal valves on inspiration due to loss of tone in the dilator nares muscle.

Static asymmetry of the face should be assessed, including midline shift of the philtrum, the depth of the nasolabial folds, jowling and the presence of platysmal bands (often present on the paralyzed side). Static asymmetry of the oral commissures is noted and the presence of hypertonicity on the each side of the face is assessed. Active movements are then assessed: excursion of the oral commissures is measured and the degree of synkinesis. The lower teeth are examined with regard to how much they show during smiling; the smile is classified using the Rubin Smile Classification.[7]

INVESTIGATIONS

Imaging of the facial nerve may be useful in delineating the site of neural injury. Indications include recurrent, progressive or persistent paralysis, trauma and suspected nerve involvement in systemic diseases.

Magnetic resonance imaging (MRI) is the only modality that demonstrates the facial nerve comprehensively from the pons to the parotid gland; with gadolinium enhancement it is capable of showing inflammatory changes. High resolution CT of temporal bone makes it possible to see

TABLE 95.3 Sunnybrook facial grading system

Resting Symmetry

Compared to normal side

Eye (choose one only)
- normal 0
- narrow 1
- wide 1
- eyelid surgery 1

Cheek (naso-lablal fild)
- normal 0
- absent 2
- less pronounced 1
- more pronounced 1

Mouth
- normal 0
- corner dropped 1
- corner pulled up/out 1

Total ☐

Resting symmetry score: Total X 5 ☐

Patient's name

Dx

Date

Symmetry of Voluntary Movement

Degree of muscle EXCURSION compared to normal side

Standard Expressions	Unable to initiate movement/SS movement	Initiates slight movement	Initiated movement with mild excursion	Movement simest complete	Movement complete	
Forehead Wrinkle (FRO)	1	2	3	4	5	☐
Gentle eye closure (OCS)	1	2	3	4	5	☐
Open mouth smile (ZYG/RIS)	1	2	3	4	5	☐
Snarl (LLA/LLS)	1	2	3	4	5	☐
Lip Pucker (OOS/OOI)	1	2	3	4	5	☐

Gross Asymmetry	Severe Asymmetry	Moderate Asymmetry	Mild Asymmetry	Normal symmetry	Total
					☐

Voluntary movement score: Total X 4 ☐

Synkinesis

Rate the degree of INVOLUNTARY MUSCLE CONTRACTION associated with each expression

	NONE: No synkinesis or mass movement	**MILD:** Slight synkinesis	**MODERATE:** Obvious but not disfiguring synkinesis	**SEVERE:** Disfiguring synkinesis Gross mass movement of several muscles	
Forehead Wrinkle (FRO)	0	1	2	3	☐
Gentle eye closure (OCS)	0	1	2	3	☐
Open mouth smile (ZYG/RIS)	0	1	2	3	☐
Snarl (LLA/LLS)	0	1	2	3	☐
Lip Pucker (OOS/OOI)	0	1	2	3	☐

Synkinesis score: Total ☐

Vol mov't score ☐ – Resting symmetry score ☐ – Synk score ☐ = Composite score ☐

bony detail and is ideal when facial nerve involvement is in the middle ear cleft.

Electrophysiological tests allow objective assessment of function, even in children.[8] Typically testing is delayed until 72 hours post onset of paralysis (to allow for Wallerian degeneration). This can be repeated every 3–5 days up to 21 days until a trend or confirmation can be obtained. The most clinically helpful use of this test is objectively to assess facial nerve function, once spontaneous motion is lost in acquired paralysis or if it had never been seen in congenital paralysis. The authors maintain that the test is not an absolute predictor for return of function but that the added data, when used with clinical information, make assessment of prognosis more rational.

TIMING OF REPAIR

For reinnervation procedures to be considered the ipsilateral facial nucleus must have an adequate number of functioning cell bodies, the proximal nerve segment must be in continuity with the facial nucleus and be able to support axial regeneration, and the distal nerve segment must be in contact with functioning muscle units and be capable of accepting regenerating neurons.[9]

Immediate or early repair of nerve injuries should always be repaired if at all possible. Primary repair of the facial nerve should be performed using an operating miscroscope if possible. Epineural repair using 9/0 nylon is as successful as fascicular repair.[10] Fibrin glue may also be used.[11]

Interposition graft

Interposition grafts are used when there is an insufficient length of nerve to allow a tension free anastomosis. The length of a graft should exceed the gap by 3–5 mm on each side.[12] The commonest donor nerves are the greater auricular nerve and the sural nerve. The greater auricular nerve usually lies within the surgical field; however, only about 5 cm graft length is available. The sural nerve has the advantage of providing a long segment of nerve and has a reliable course, allowing ease of location. Disadvantages include a potentially larger diameter and higher neural to connective tissue ratio.[4] In one series 95% of patients had some return of function following interposition graft and success has also been described in patients who have had postoperative radiotherapy.[13]

Atrophy of muscle and degeneration of motor end plates begins to occur following denervation of facial muscles. There is little prospect of successful reinnervation after

2 years.[14, 15] As it may take 6–9 months for nerve regeneration to occur following nerve transfer, this must be taken into account when evaluating the likelihood of success of a nerve transfer.

TREATMENT PLANNING

Treatment should be individualized. However, aims of treatment are:

- the protection of the eye
- to provide symmetry at rest
- correction of synkinesis
- to provide oral continence
- to provide dynamic facial movement
- to improve speech
- to improve nasal deviation and airway patency.

NON-SURGICAL MANAGEMENT

Non-surgical management of the eye

Non-surgical strategies to protect the eye are used whilst waiting for a damaged facial nerve to recover or sometimes, in a well-motivated patient, as a permanent solution for the eye as an alternative to surgery. The aim is to prevent exposure dermatitis of the corneal leading to ulceration and blindness. Adequate provision of ocular lubricants during the day is essential and the patient must be taught how to tape the lids closed at night to prevent desiccation. Eye irritation mandates ophthalmology review.

Non-surgical treatment of the face

The cornerstone of management of facial paralysis is facial therapy.

Neuromuscular retraining by an experienced therapist can improve aberrant activity on the unaffected side, and the treatment of synkinesis and hypertonicity (if present) on the affected side. A variety of treatment modalities are used, including biofeedback, electromyography and self-directed mirror exercises.[16]

Strong consensus exists as to the importance of facial therapy in the multidisciplinary management of facial palsy. Some evidence exists that tailored facial exercises can help to improve facial function, mainly for people with moderate paralysis and chronic cases, and reduces recovery time and negative sequelae in acute cases.[17]

SURGICAL MANAGEMENT

Brow

In the young, paralysis of one side of the forehead causes relatively minimal problems. They have no forehead crease lines, so the difference between each side of the face is only noticed on animation. The eyebrow does not descend since there is still some elasticity in the tissues. In a 20-year-old man, the animation of one side of the forehead may be considered an embarrassment as it draws attention to the overall asymmetry of the face. Botulinum toxin injections to contralateral frontalis may be employed after careful discussion with, and thorough understanding by, the patient.

In later life, with loss of skin elasticity, the eyebrow sometimes descends, taking part of the eyelid skin with it, so that vision may be partially obstructed. A direct brow lift provides long-lasting correction. Other brow-lifting techniques, used in cosmetic surgery, include endoscopic brow-lifts and transblepharoplasty brow-pexy techniques using implants. These may be useful in correcting small ptoses in partial facial weakness but have limited application in profound facial palsy, particularly in the elderly.[18] More sophisticated transfers of muscle groups, for example from the contralateral frontalis muscle, do not seem to be particularly reliable, which probably relates to devascularization of the muscle fibres.

Upper eyelid

In congenital unilateral facial palsy, even if the young patient does not close their eye perfectly they seem to have minimal problems with exposure keratitis. The child passes through a phase before the age of 3 when excess epiphora may cause them to rub their eye and develop pseudo-conjunctivitis. Eventually they learn to avoid this and by the age of 4 seem to have no further problems. Upper lid weighting is not required and indeed is actively disliked by the child as it may narrow the palpebral fissure and sometimes interfere with their visual field compared to the normal contralateral side.

As the patient with congenital unilateral facial palsy reaches their mid-20s, the lower eyelid descends and scleral show may be apparent. A McLaughlin's lateral tarsorrhaphy is an effective and aesthetic means to elevate the lower eyelid, slightly narrow the palpebral fissure and restore symmetry.

However, a unilateral facial palsy developing in adulthood is a different matter and avoidance of exposure keratitis is mandatory. Even if recovery is expected, the eye must be protected by creams at night, tape closure or surgery. There are numerous methods available to protect the cornea. The principle is to either allow the upper eyelid to drop, elevate the lower, or both. On blinking, the levator palpebrae relaxes and, if the upper eyelid is either loaded or sprung, the eyelid can be persuaded to close. Specially made gold weights, smoothly rounded and capable of fixation to the tarsal plate, are easy to insert and largely reliable. Fixation to the tarsal plate is essential as it significantly reduces extrusion and migration. It is desirable to use as light a weight as will effectively close the eye, and rarely is more than 1 g required (1.5 g gold weights are heavy and eventually the levator is apt to weaken, producing ptosis). Closure sufficient to cover the cornea is reported in 78% of cases with resolution of keratitis in 62–100% of cases.[9, 19–21]

Other methods of treating lagopthalmos include: lengthening the levator by division or inserting a strip of temporalis fascia; insertion of magnets in upper and lower lids;[22] and the Morel-Fatio palpebral spring.[22, 23]

The classic Gillies procedure – the transfer of slips of temporalis muscle and deep temporal fascia to upper and lower eyelids – has been used extensively in the past. It has now fallen out of favour due to unpredictability of result compared with the simpler and more predictable lid loading techniques described above.

Lower eyelid

Elevation of the lower eyelid may be required where there is a scleral show beneath the limbus of the eye, and to correct epiphora. Many methods are available to achieve this, but a McLaughlin's lateral tarsorrhaphy is aesthetic and effective for minor degrees; however, large procedures narrow the palpebral fissure and are extremely unaesthetic. If this is unsuccessful or the depression is more severe, then a palmaris tendon sling between the medial canthal ligament and the supraorbital margin laterally can provide good elevation. Conchal cartilage grafts may be used to support the lower eyelid, set between the infraorbital margin and the lower edge of the tarsal plate.[24]

The treatment of epiphora remains challenging. The massaging action of the orbicularis on the tear flow and its siphoning effect on the lachrymal sac is important, as is the position of the lower lateral canaliculus in respect of the orbit. However, a perfectly positioned lachrymal canaliculus does not mitigate against a watering eye. Overproduction of tears by reducing the inhibition on the secretor motor fibres to the lachrymal sac via the greater superficial petrosal nerve may be an unwanted factor.

The Gillies procedure, involving transferring the temporalis muscle and extending it by using the temporalis fascia passed through the upper and lower eyelids, is less popular these days, although, if perfectly tensioned, satisfactory results can be achieved using this technique. It is probably less reliable than the methods mentioned previously.

Nasal airway

Paralysis of the nasalis, dilator nares and levator labii aleque nasi muscles may lead to collapse of the external and internal nasal valves. This may be exacerbated if the nose is pulled towards the unaffected side by the unopposed action of the contralateral facial muscles. The airway is narrowed with reduction in airflow. If the patient is symptomatic, elevation of the nasal base by tendon slings fixed to the maxillary periosteum is effective. Septal deviations, if present, should be corrected. Insertion of supportive cartilage grafts to the alar rim have also been used.

Upper lip and cheek (smile reconstruction)

The majority of patients presenting with refractory facial paralysis do so for correction of facial asymmetry and/or the restoration of dynamic facial movement. For those patients who simply want to look symmetrical in photographs and/or are either not a candidate for more complex procedures or for whom a prolonged recovery and period of facial rehabilitation is not attractive, then static facial slings can restore a surprising degree of resting facial symmetry.

STATIC TECHNIQUES

Facia lata, harvested from the lateral thigh, is commonly used in this application, although some proponents prefer tendon grafts of plantaris or palmaris longus as they are said to stretch less over time. The grafts are inserted into the corner of the mouth at the nasolabial fold and anchored either to the deep temporal fossa or zygomatic periosteum using either permanent sutures or Mitek® Bone Anchors. Using the contralateral normal side as a guide to assess the vector required, the grafts are inserted with sufficient tension to just overcorrect the asymmetry to allow for post-operative relaxation.

DYNAMIC TECHNIQUES

Regional muscle transfers

Dynamic muscle transfers have traditionally involved the transfer of muscle of mastication to the mouth to replace the lost activity of levator anguli oris and zygomaticus major and minor muscles. Regional muscle transfers have the advantage of immediate results as no reinnervation is required; however, the transfer of a regional muscle produces a voluntary smile rather than a natural spontaneous smile, and abnormal movements can be produced during chewing. Transfer of the masseter muscle produces little in the way of movement of the mouth and an unsightly bulge in the cheek. Temporalis transfer, popularized by Gillies, involved the turnover of strips of temporalis muscle and deep temporal fascia over the zygoma and inset into the corner of the mouth and/or the eyelids. This may produce an unsightly bulge over the zygoma. More recently a prograde temporalis transfer, described by Labbé and Huault, has become popular.[25]

In recent years the use of regional muscle transfers has largely been superceded by free muscle transfers.

Free muscle transfers

Microsurgical functioning muscle transfer has become the mainstay of facial reanimation in the developed world over the past three decades. Pre-operative planning is essential – assessment of the vector and magnitude of the smile on the normal side must be made to plan. A variety of muscles have been described for facial reanimation but the most popular remain the gracilis muscle and the pectoralis minor muscle. To produce a voluntary smile requires the use of the VIIth nerve, most commonly by way of a cross-facial nerve graft.

Single stage muscle flaps with innervation from the contralateral facial nerve have been reported. This technique requires the use of a muscle flap with a long nerve segment, such as latissimus dorsi or rectus abdominis.[26]

A comprehensive exploration of the branches of the contralateral facial nerve is performed at a first stage. Usually a redundant buccal branch is selected as the donor nerve, using bipolar nerve stimulation. A sural nerve graft, harvested from the leg, is placed onto a redundant buccal branch and tunnelled across the midline to the paralyzed side of the face. Growth of the facial nerve is followed clinically by way of Tinel's sign and, following successful regeneration, a free functioning muscle transfer is performed 6–9 months later at a second stage. The muscle is inset into the nasolabial fold and commissure of the mouth and revascularized using either the facial vessels or the superficial temporal vessels.

The use of the masseteric branch of the Vth cranial nerve to power muscle transplants in a single operative stage has recently become used. Advocates of the masseteric nerve cite benefits of a single-stage procedure, a greater axonal load that can be delivered to the muscle resulting in a stronger contraction of the transplanted muscle – a more normal excursion of the mouth and preservation of the contralateral facial nerve.[27] These combine to allow a more normal reconstructed smile. The disadvantage is the need to relearn to smile by biting.

The use of cross-facial nerve grafts and other donor nerves to power the transplant or reinnervate intact facial musculature depends on the goals of treatment and patient factors. Although initially thought that only a cross-facial nerve graft could produce spontaneous facial activity, spontaneous activity has been observed in a significant proportion of transplants innervated by the nerve to masseter.[28, 29] This has been ascribed to the phenomenon of cortical plasticity; however, activity of the normal masseteric nerve during smiling has been observed on EMG studies, and this may offer an alternative explanation.

Lower lip

Transfer of the anterior belly of digastric muscle[30] and platysmal muscle[31] have been described for dynamic reanimation of the lower lip. The results of these are variable. A simpler and more predictable result can be achieved by the selective weakening of the contralateral depressor labii inferioris muscle. This can be achieved temporarily by the use of Botox or more permanently by direct excision of the muscle through an intra-oral approach.[32, 33]

ADJUNCTS

Other cosmetic interventions may be performed as required, including facelifts, midface lifts, rhinoplasty and correction of platysmal bands.

KEY POINTS

- A diagnosis of idiopathic Bell's palsy should only be made with a classical history – any atypical clinical features should prompt further investigation to exclude another cause.
- Facial paralysis should be managed in a multidisciplinary fashion.
- Reinnervation can only be successful for approximately 18 months following onset of facial paralysis.
- Early intervention to protect the eye may be required.
- Facial reanimation can be vey effective but a completely normal appearance is rarely achieved.

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CHAPTER 96

PARTIAL AND TOTAL EAR RECONSTRUCTION

Cher Bing Chuo

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SEARCH STRATEGY

Data in this chapter may be updated by a Medline search using the keywords: partial and total ear reconstruction, and total and partial auricular reconstruction. It is focused on a narrow range of common partial ear reconstruction techniques and the basic principles guiding total ear reconstruction.

INTRODUCTION

The external ear is a convoluted 3D structure with a vestigial function to gather sound waves towards the external auditory meatus (EAM). This delicate structure with a complex contour has become a subject of beauty over the ages. There has been increasing awareness that individuals desire the appearance of a pair of symmetric, aesthetically pleasing ears. In a representative proportion of the UK general population, the awareness of perceived differences in the appearance of their ears has led to self-consciousness or increased sensitivity to these differences.[1] Reconstructive surgeons should have comprehensive knowledge of normal ear anatomy in order to perform accurate and aesthetic auricular reconstruction.

ANATOMY

Surface anatomy

Auricular surface anatomy is characterized by a series of ridges and depressions (**Figure 96.1**).[2] The outer border of the upper two-thirds of the ear is framed by the elevated helix. Darwin's tubercle is a prominence that sits on the posterior upper helix. The crus or root of the helix slopes downwards and curves posteriorly from the anterior upper third of the ear, over the superior aspect of the EAM. This ridge separates the conchal depression into the upper cymba concha and lower cavum concha. A complex elevation – the antihelix, separates the wide and deep concha from the narrow and shallow scaphal depression. The upper part of the antihelix follows the curve of the outer helix before dividing to form 'V-shaped' delicate ridges called the superior and inferior crura. These crura border a depression called the triangular fossa. The antihelical elevation extends towards the ear lobule to meet a short semicircular ridge – the antitragus – which is separated from the tragus by the more inferiorly placed intertragic notch or incisura. The tragus is a prominent quadrangular ridge which points posteriorly and lies over the anterior aspect of the EAM. The flat ear lobule sits inferior to the tail of the helix at the lower quarter of the ear, below the antitragus and the incisura. On the medial (cranial) surface of the auricle, the scaphal and conchal eminences are convexities that correspond to the scaphal and conchal depressions on the lateral surface described previously. The conchal eminence meets with the mastoid process to form the postauricular sulcus.

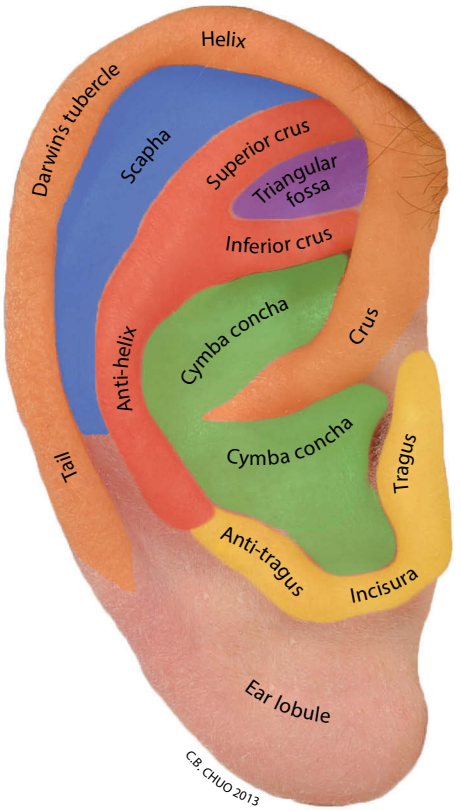

Figure 96.1 Lateral surface of the external ear. The locations and proportions of the key structures including the ear lobule are shown. Important ridges are the helix, antihelix, tragus and antitragal complex. Important depressions are the scapha, concha and triangular fossa.

Posture and position

The posture and position of the ear are shown in **Figure 96.2**.[3–7] The longitudinal axis of the ear is considered by Tolleth as the 'line of balance' that extends from the fullest point on the upper helical border to the most dependent point on the lower border of the ear lobule. It lies posteriorly rotated from the vertical axis of the head by 15–30 degrees. The axis of the ear may sometimes lie parallel to the dorsum of the nose, but more frequently lies 12–15 degrees more vertical than the nasal dorsum.

The ear is sited approximately the length of an ear, measured along its longitudinal axis, posterior to the lateral orbital margin. In 85% of individuals, the upper border of the ear is level with the most lateral point of the eyebrow.

The lateral surface of the ear is turned anteriorly with a conchomastoid angle of 30 degrees and a concho scaphoid angle of 90 ± 15 degrees. The most prominent point of the ear sits 17–20 mm lateral to the side of the head in the horizontal plane.

Three key measurements are required in order to site the reconstructed ear in an aesthetic and symmetric position: an appropriate angle of rotation for the longitudinal axis, the vertical level for the upper border of the ear and the horizontal distance of the ear from the lateral orbital margin.

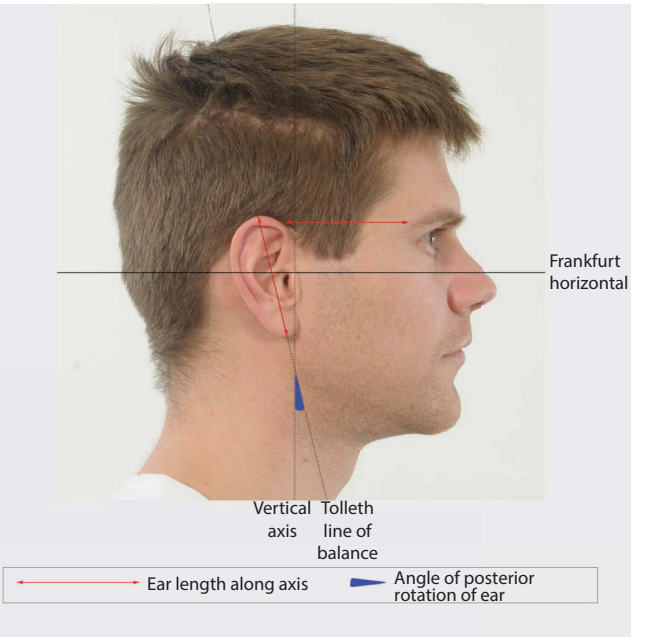

Figure 96.2 Lateral aspect of the head. This illustrates the ideal position of the upper external auditory meatus in line with the Frankfurt horizontal and the anterior border of the helix positioned one ear length posterior to the lateral orbital margin. The longitudinal axis of the ear is posteriorly rotated relative to the vertical axis of the head.

Proportions

The normal adult ear measured along its longitudinal axis is 63–65mm and the width of the ear is 50–65% (mean 55%) of its length (**Figure 96.3**).[3, 5, 8]

The triangular conchal depression has a width two-thirds of its length. The average length of the ear lobule as measured from the lowermost incisura to the most dependent point on the lower border of the ear lobule is 18 mm, and the ratio of lobule length to full ear length is 0.28–0.30.

Structure

Mechanical strength to maintain the structure of the external ear is provided by fibrocartilage which extends from the helix to the incisura.[2, 9–11] At the anterior aspect of the concha, a cartilaginous cylinder continues from the EAM medially to form the outer third of the external auditory canal. The auricular cartilage is attached to the temporal bone by two ligaments. The anterior ligament holds the tragus and anterior helical crus to the root of the zygomatic arch. A posterior ligament holds the medial conchal eminence to the lateral mastoid process.

Six vestigial intrinsic and three extrinsic muscles attach to the perichondrium of the ear. The extrinsic muscles auricularis anterior and superior attach to the galeal aponeurosis, and the auricularis posterior attaches to the periosteum at the base of the mastoid.

The skin on the lateral surface of the ear is thin and binds tightly to the underlying perichondrium encasing

the fibrocartilage. This allows the details of the complex convolutions of the cartilage to be easily seen.

Skin on the medial surface of the ear is mobile, with a thickness of 0.4–0.8 mm. There is minimal subcutaneous adipose tissue and extensive fatty infiltration of the dermis, beginning at the level of the sebaceous glands, and increasing in density with depth. A loose areolar fascial plane lies between the perichondrium and subcutaneous fat. This well-vascularized layer is a continuation of the intrinsic muscles of the ear, and contributes to the mobility of the postauricular skin.

The ear lobule is a soft fibro-fatty cutaneous flap that is suspended from the lower border of the auricular cartilage.

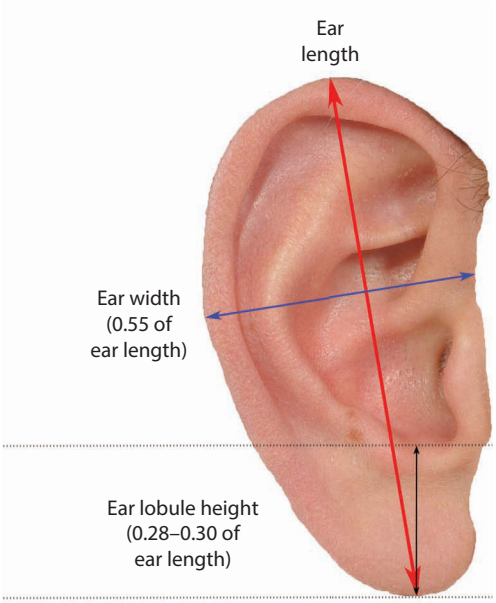

Figure 96.3 Lateral surface of the external ear in its natural orientation. Note the width-to-length ratio of the ear and the height of the ear lobule relative to total ear length.

Blood supply

The ear is supplied by the superficial temporal artery (STA) and the posterior auricular artery (PAA).[2, 9, 11–15] The STA ascends in the preauricular area through the parotid gland and gives rise to one to three branches to the ear. The lower branch supplies the lower margin of the ear lobule, the middle branch the tragus, and the upper branch the ascending helix and the triangular fossa–scapha arterial network. After supplying the ear, the STA ascends to form two terminal branches about 3 cm above the zygomatic arch – the anterior (frontal) and posterior (parietal) branch. These branches supply a fascial layer – the temporoparietal fascia (also called the superficial temporal fascia). This lies superficial to the deep temporal fascia layer, which is supplied by the middle temporal artery – a branch of the STA that arises 1–3 cm below the upper border of the zygomatic arch. See **Figure 96.4**.

The PAA travels towards the scalp in the groove between the mastoid and the cartilage of the posterior EAM, and then continues onto the conchal eminence.

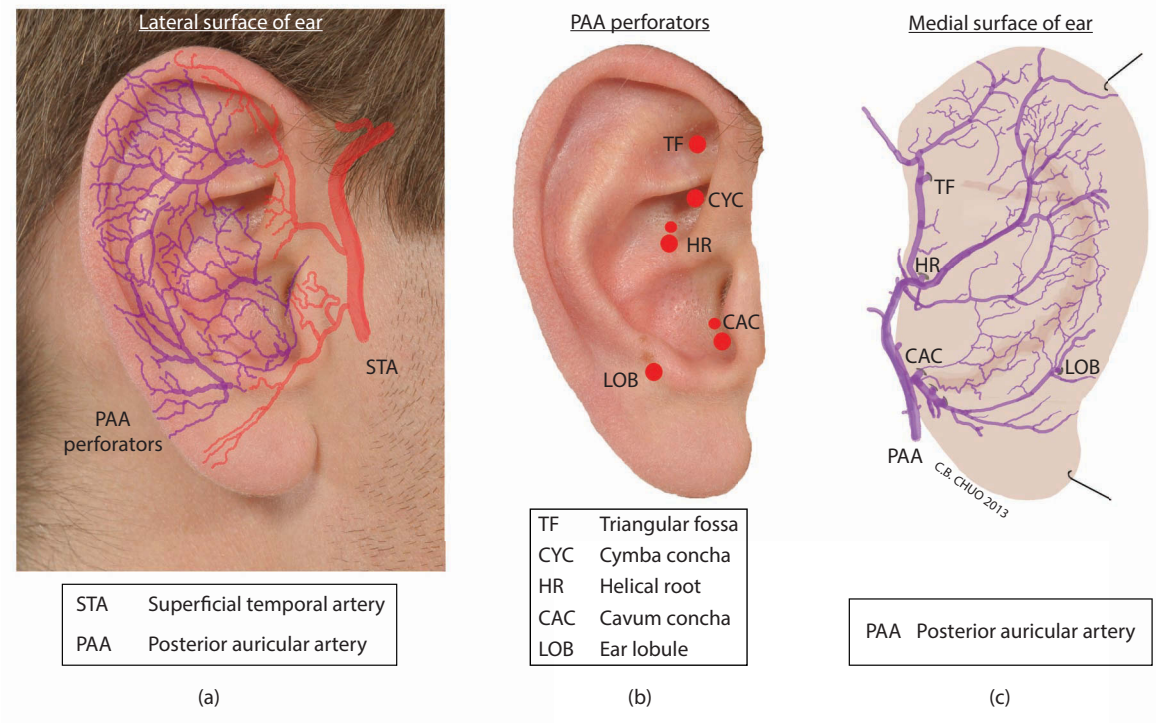

Figure 96.4 The pattern of distribution of the two key arterial networks that supply the skin of the external ear. The superficial temporal artery (STA) provides input to limited areas of the anterior and inferior aspect of the lateral surface, and the remaining ear is supplied by the posterior auricular artery (PAA). Vessels from the PAA perforating the ear cartilage provide a means of communication between the two arterial networks on the lateral and medial surfaces of the ear.

The lower division supplies the posterior surface of the ear lobule, minor posterior branches supply the mastoid fascia and the middle and upper divisions supply the middle and upper thirds of the medial surface of the ear. Perforating branches of the PAA form during its course over the medial surface of the concha. These traverse the cartilage and supply the lateral surface of the ear at key areas: the outer border of the antitragus, cavum concha, helical crus, cymba concha and triangular fossa.

Two main arterial networks formed by communicating branches from the STA and PAA are present on the lateral surface of the ear. The triangular fossa–scapha network is primarily formed from the STA and the conchal network is dominated by perforating branches of the PAA. The upper branch of the STA also communicates with the upper division of the PAA on the superior medial surface of the ear. These networks supply the skin via well-developed subpapillary (intradermal) and the subdermal plexus.

The venous drainage of the ear via the superficial temporal system is variable, whereas the drainage to the posterior auricular system is predictable via the venae comitantes accompanying the PAA.

EAR RECONSTRUCTION

A number of factors need to be considered to determine the most appropriate technique of reconstruction in patients who have congenital and acquired ear deformities and defects. The reconstructive surgeon needs to understand the aetiology of the defects and whether cartilage and/or skin are involved in partial ear defects. Account needs to be taken of whether ear deformities are unilateral or bilateral, the condition of the soft tissues local to the site of the intended reconstruction, the degree of function of the middle and inner ear, the age of the patient, the availability of costal cartilage for framework construction and the patient's preferences for reconstruction.

Indications for ear reconstruction

Patients with complex congenital ear deformities, including those with microtia and anotia, are candidates for total ear reconstruction. Partial ear reconstruction may be indicated in congenital (e.g. lop ear deformity) and acquired deformities involving up to two-thirds of the ear. Trauma (e.g. bite injuries, avulsions and burns) and cancer are common causes of acquired partial or total ear loss requiring ear reconstruction.

Multidisciplinary care

Ear reconstruction is best managed within the setting of a multidisciplinary team comprising plastic surgeons, maxillofacial prosthetists, otolaryngologists, audiologists, radiologists, clinical psychologists and speech and language therapists. This allows the patient and their family to be provided with all possible avenues for reconstruction including prosthetic and autologous ear reconstruction. Imaging of the ear and options for optimizing hearing in patients with hearing loss can also be offered. Clinical psychologists are able to counsel patients with pre-existing psychiatric conditions and assist with the management of patient expectations for future reconstruction.

Surgical goals of ear reconstruction

The aim of total ear reconstruction is to create a contoured replacement structure, with natural proportions, located and orientated in an ideal position on the side of the head. This should appear symmetrical in appearance and location to the opposite normal ear if the reconstruction is unilateral. It is particularly important to replicate key features of the surface anatomy of the lateral ear. The reconstructed ear should also be elevated posteriorly away from the side of the head, to produce symmetrical ear projection and to re-create a post-auricular sulcus.

In practice, the individual aesthetic preference of the patient, the desire for and acceptance of a longer recovery time required for autologous reconstruction influence the agreed plan for correction of the ear deficit or deformity. Furthermore, any autologous reconstruction that is offered is tempered by the need for and available options for structural replacement and soft tissue cover.

Clinical assessment

As part of their clinical assessment[16] the multidisciplinary team should note the patient's general medical health and medications. Medical history of cardiorespiratory disease, diabetes, hypertension and immunodeficiency need to be considered in terms of fitness for surgery and the risk of complications afterwards. Use of aspirin, steroids, warfarin, immunosuppressive agents, tobacco and recreational drugs are documented. Previous procedures on the ears and chest, including operations for ear reconstruction, are noted. A history of hypertrophic or keloid scarring is sought. Previous or current psychiatric history may influence the patient's perception of his or her condition and must be documented.

Specific assessment for ear reconstruction is made in these key areas:

- size, nature and location of the ear defect or deformity
- whether defects or deformities are unilateral or bilateral
- symmetry of the size, shape, appearance of the lateral surface of the ear, angle of reclination (rotation from the vertical) and elevation or projection of the ear
- availability and condition of local and regional vascularized tissues for soft-tissue reconstruction
- availability and condition of donor conchal and costal cartilage for structural reconstruction
- audiology assessment
- assessment by a prosthetist
- patient expectations and preferences
- age of the child in congenital deformities.

Clinical photographs of both ears in close-up and in standard frontal, oblique and lateral facial views are taken to document the condition. The size of any partial defect is

measured and the site described in relation to the upper, middle and lower thirds of the ear, and a note is made of key aesthetic contours which are affected. In unilateral deficits, key aspects of the normal ear are measured – ear height, width, angle of reclination and horizontal distance from the lateral canthus. Any deficiency of cartilage structural support or overlying skin is identified. The presence of scars and the quality of the skin over and adjacent to the site of intended reconstruction influence the options available for reconstruction. The STA is palpated along its course to the frontal and parietal branches. Primary sources of cartilage graft for replacement of structural support and framework construction are conchal and costal cartilage. The chest is examined for the presence of scars and the contour of the costal margin. Contralateral ears are examined for the availability of conchal cartilage for unilateral partial reconstruction.

An assessment by the maxillofacial prosthetist is carried out to present the patient with the available prosthetic options for the individual defect or deformity. This may range from osseointegrated implant-based to adhesive-based silastic devices. The required care and maintenance regimen for these prosthetics is described. If autologous ear reconstruction is desired, moulds of the affected and unaffected ears are taken to produce 3D silicone models for planning surgical reconstruction.

The reconstructive preference of the patient is sought, and his or her expectation of the outcome of surgery is evaluated against the achievable result. Unrealistic expectations of the outcome of reconstructive surgery are a relative contraindication to proceed. Caution against surgery is also advised in patients who exhibit symptoms of body dysmorphic disorder (BDD) and untreated psychiatric conditions.[16]

Special investigations and planning

A chest radiograph is helpful for reviewing the configuration of the ribs in conjunction with the clinical assessment of the costal margin, especially if the patient has had previous chest trauma or thoracic surgery. Patients with extensive local scarring may require a temporoparietal fascial flap as vascularized soft-tissue cover for ear reconstruction. Angiography of the external carotid artery or Doppler ultrasonography is important for assessing the continuity and calibre of the STA.

Two-dimensional templates and 3D models are important for the planning of partial and total ear reconstruction. Templates are typically made from radiographic or acetate film. These may be customized by tracing the outer border, antihelix, superior and inferior crus, tragus and antitragus of the contralateral normal ear (**Figure 96.5**).[17, 18] These images are then reversed to create a basis on which to plan reconstruction. Nagata has designed a series of standardized templates for cartilage framework construction based on key height and width measurements, and Tolleth's described proportions of the ideal ear.[19] An appropriate standardized template for an individual patient is chosen based on the height of the contralateral normal ear (**Figure 96.6**).

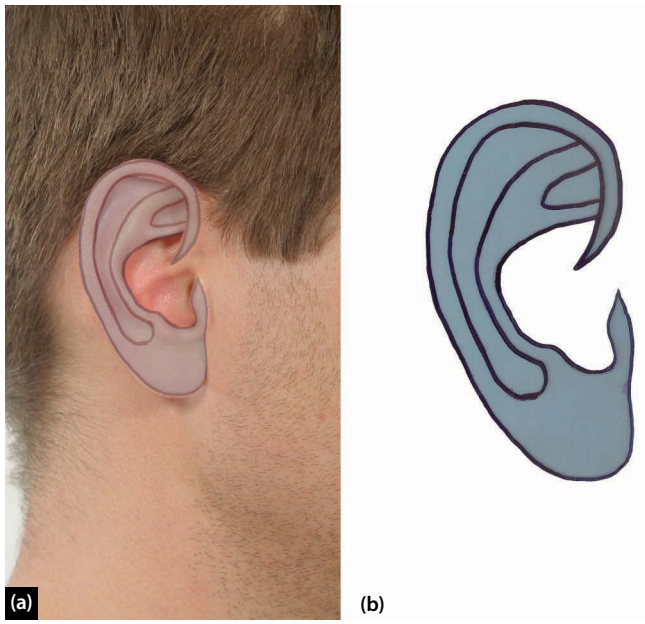

Figure 96.5 **(a)** Customized 2D template, drawn on a semi-transparent film, that highlights the key structures of the ear described in Figure 96.1. **(b)** Overlay of the template on the ear to show that the template provides an accurate depiction of the size and proportions of the ear. The customized template taken from the remaining normal ear and reversed is useful in patients where unilateral reconstruction is required.

Customized templates are helpful in assessing partial ear defects and for unilateral total ear reconstruction. Standardized templates are less sympathetic to the individual features of the contralateral normal ear but support the fabrication of frameworks that can be replicated time and again, and they are helpful in providing a basis for bilateral total ear reconstruction.

Three-dimensional silicone models are made by taking an impression of and replicating the contralateral normal ear, and then creating a mirror image of this model. These models not only recreate the complex depressions and ridges on the lateral surface of the ear but also provide additional information on the degree of projection of the ear. Both templates and models can be sterilized for use intra-operatively as a guide for cartilage framework fabrication and surgical incision design for the creation of soft-tissue cover over the framework.

Principles of ear reconstruction surgery

Partial ear reconstruction may require the replacement of one or both components of cartilage and skin cover. Cartilage support is more important in defects affecting areas that provide length or width stability for the ear framework, such as the helix and antihelix. In addition, cartilage replacement in highly contoured areas on the lateral surface of the ear improves the aesthetic appearance of the reconstruction. Isolated cartilage loss in the concha causes minimal framework instability, hence conchal cartilage is often a preferred source of grafts for reconstruction of small defects.

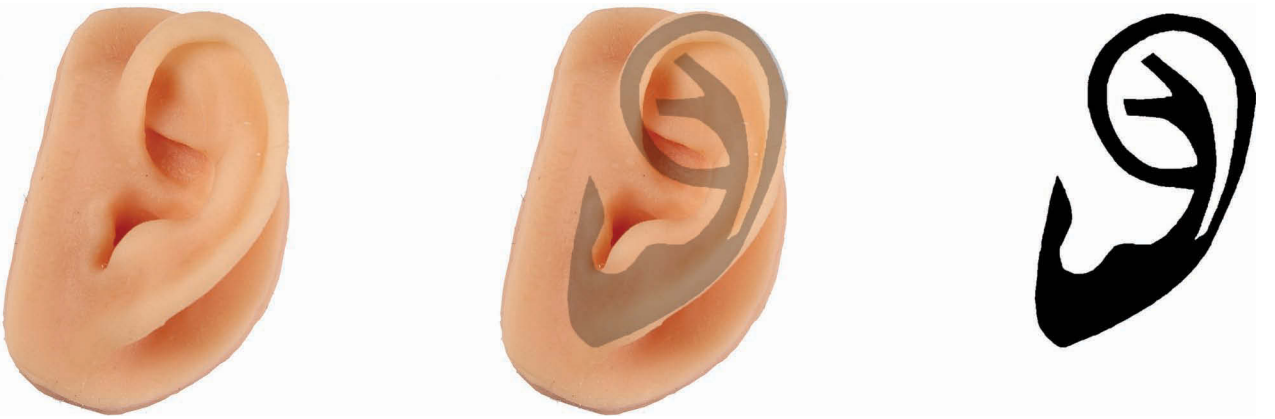

Figure 96.6 **(a)** Standardized 2D template, with the position and proportions of key structures as described for the ideal ear according to Tolleth.[3] **(b)** Silastic 3D model produced from the remaining normal ear in a patient with unilateral deformity. This may be reversed to act as an intra-operative model during reconstruction. **(c)** Overlay of the template on the ear model to show that the standardized template, although well-proportioned, may not accurately reflect the appearance of the contralateral normal ear.

Costal cartilage is available in larger volume and provides much higher structural rigidity than conchal cartilage. It is thus ideal for framework fabrication in total and subtotal partial ear reconstruction as it is able to withstand the deformational forces generated by scar contracture of the skin and soft tissue used for draping the framework.

Alloplastic materials such as shaped silastic and high-density porous polyethylene implants are also able to provide good mechanical strength when used as support in ear reconstruction. However, the use of silastic ear implants is associated with a significant risk of implant exposure and infection and is therefore not recommended.[20, 21] Porous polyethylene (Medpor®) is a biocompatible material that allows host tissue ingrowth for better tissue integration, but it has also been shown to have a high exposure rate of 44% unless fully enveloped by a large well-vascularized temporoparietal fascial flap, decreasing the rate of exposure to 7%.[22] These implants are also prone to fracture which may be difficult to detect.

Defects of skin only on the medial (cephalic) surface of the ear can usually be repaired by direct advancement of the mobile skin in this area of the ear (see 'Structure' above). A consequence of significant skin advancement in this area is a decrease in projection of the ear, loss of the postauricular sulcus and ear asymmetry. Skin on the lateral surface of the ear is adherent to the underlying perichondrium, thus traumatic lacerations and cancer excisions in this area tend to cause cartilage exposure. Skin defects in this area may be reconstructed by converting it to a full-thickness defect that is closed directly (e.g. a wedge excision if the defect is sited at the helical rim). Alternatively, the underlying cartilage may be excised (e.g. if the defect is sited at the scapha or concha) to produce a vascular bed suitable for a full-thickness skin graft. Skin grafts are ideally harvested from the head and neck area for a better colour match. Caution should be paid to cartilage excision in this way, as there is a high risk of causing a secondary ear deformity if medium to large sections of cartilage are removed which compromise the structural support of the ear.

Skin-cartilage defects and full-thickness defects of the ear may be reconstructed with local, random-pattern cutaneous or chondrocutaneous flaps, which may be used in combination with a structural framework. For example, a large, full-thickness middle-third defect involving the helix and antihelix requires the replacement of contoured cartilage support and flap cover for more than twice the surface area of the skin deficiency. This provides skin cover for the medial surface of the framework, as well as taking into account the increased area required for draping over the ridges and depressions of the lateral surface.

Patients undergoing subtotal and total ear reconstruction require skin or fascial flaps over the ear framework which provides vascularized soft-tissue cover. The amount of cover needed depends on the height, width and depth (thickness) of the framework constructed. A more complex and detailed framework exhibits more anatomically accurate features and may include a conchal bowl, which increases the thickness of the frame and hence the surface area of the soft-tissue cover required. The local hairless mastoid skin at the site of intended reconstruction is the workhorse for frame cover. When this is not available (e.g. in burns) or limited (e.g. in patients with low hairline), then the temporoparietal fascial flap with an overlying skin graft is used to cover the lateral surface of the framework. Usually, there is insufficient vascularized soft tissue to envelope both the lateral and medial surfaces of the framework adequately in a single procedure. Ear reconstruction is therefore often staged and provision of soft-tissue cover for the less visible medial surface is left for a later procedure.

It is essential for skin or fascial flap cover to be well-vascularized, as autologous cartilage frameworks are large avascular grafts containing chondrocytes that rely on the surrounding soft tissues for nutrient and oxygen delivery. Secondary vascularization from these soft tissues also improves framework stability through fibrous scar formation and aids long-term frame retention.

Timing of ear reconstruction

The majority of paediatric ear reconstruction is indicated for congenital deformity and is a primary subtotal or total reconstructive procedure. By 5 years of age the ear of the child achieves 87% of the adult size, and by 12–13 years 98% of adult ear size is reached.[23] The complex nature of the Nagata costal cartilage framework requires a large volume of costal cartilage to fabricate the frame. He proposes that children are offered a two-stage ear reconstruction after the age of 10 years and when they achieve a horizontal chest circumference of ≥60 cm at the level of the xiphoid.[24] Brent believes that the timing of reconstruction should take into account the psychological effect of childhood teasing which starts at 7–10 years of age and the physical growth of the child until a substantial amount of costal cartilage is available.[25] He produces a simpler framework for his three- or four-stage ear reconstruction, and 40% of his patients undergo their first operation at 5–6 years and another 40% at 6–10 years of age. The ability of the child to cooperate with post-operative care is also a key factor in the choice of timing to proceed with reconstruction.

The timing of adult partial ear reconstruction depends on the size and cause of the ear defect, and on patient preference. Reconstruction after cancer excision is dependent on the clearance margins and the need for adjuvant radiotherapy. If primary autologous reconstruction is carried out immediately after tumour excision, adjuvant radiotherapy is deferred for at least 4 weeks to allow time for wound healing and vascularization of the cartilage framework. Delaying ear reconstruction for 12–24 months after cancer removal provides time for regular evaluation for locoregional recurrence in patients with high-risk tumours or narrow excision margins. Traumatic lesions after bite injuries are ideally closed or skin grafted initially due to an increased risk of wound infection. Small defects after traumatic or wide-margin cancer excision benefit from early reconstruction. If delayed reconstruction is planned, a period of 3–6 months will allow time for soft-tissue induration to subside and scarring to mature.

PARTIAL EAR RECONSTRUCTION

It is useful to classify partial defects of the lateral surface into those that affect the upper third, middle third and concha, and the lower third of the ear. Upper-third defects are easily visible and may involve the helix, superior and inferior crus, and superior antihelix, which are features that provide structural support. Priority is given to preservation of the junction of the anterior helix with the scalp, which is important for spectacle retention. Small skin-only defects in the upper third may be closed directly with minimal deformity. Medium-sized lesions may be reconstructed with local skin flaps or converted to a full-thickness triangular excision and a closing chondrocutaneous wedge performed (**Figure 96.7**). The apex of the wedge ideally extends into a depressed area of the lateral ear contour and the cartilage in this area requires debulking as part of a dog-ear reduction. Wedge excision reduces the height and changes the shape of the ear. It also tends to cause a 'cupped' appearance of the auricle, which is corrected by the use of accessory triangles at the apex. In order to minimize altering the shape and prominence of the ear, the Antia-Buch technique is used for helical lesions and advances chondrocutaneous flaps from the crus and tail of the helix into the defect (**Figure 96.8**).[26] The flap encompassing the helical crus is only mobilized using V–Y advancement if the defect is large. Large defects causing substantial loss of ear height and defects associated with the loss or deformity of the helix at the junction of the anterior helix with the temporal scalp will benefit from reconstruction with the use of a cartilage graft for support and appropriate soft-tissue cover. This complex reconstruction can be performed in one or two stages.

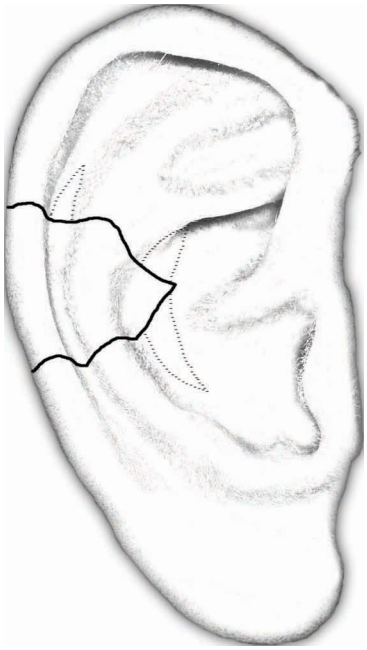

Figure 96.7 Wedge excision with refinements. The apex of the wedge ideally extends into a depressed area of the lateral ear contour and the cartilage in this area requires debulking as part of a dog-ear reduction. Wedge excision reduces the height and changes the shape of the ear. It also tends to cause a 'cupped' appearance of the auricle, which is corrected by the use of accessory triangles at the apex of the wedge.

Defects of the peripheral middle third of the ear involving the helix and antihelix, which provide structural support, are therefore treated differently from isolated defects involving the concha only. Additional cartilage support is not required if either the helical or antihelical ridges remain intact. Options for managing peripheral middle-third defects include:

- direct closure
- wedge excision and closure
- local or regional skin flaps, e.g. bipedicled tubed flap for helical defects, retroauricular (mastoid) flap of Dieffenbach[27]
- helical and conchal chondrocutaneous advancement flaps, e.g. Antia-Buch flap (**Figure 96.8**)

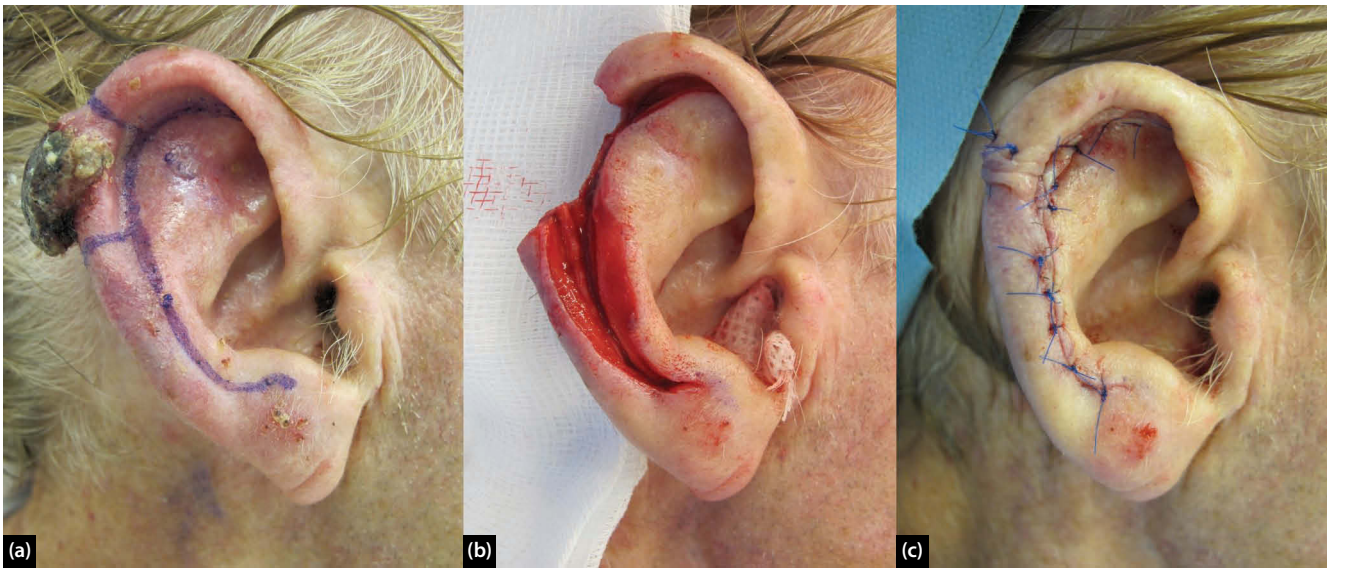

Figure 96.8 Antia-Buch helical chondrocutaneous advancement flap. This composite flap reconstruction is ideal for defects on the outer margin of the upper third of the external ear, and involves local transposition of the crus and anterior helix. Larger defects may require the additional local transposition of the tail and posterior helix, as shown.

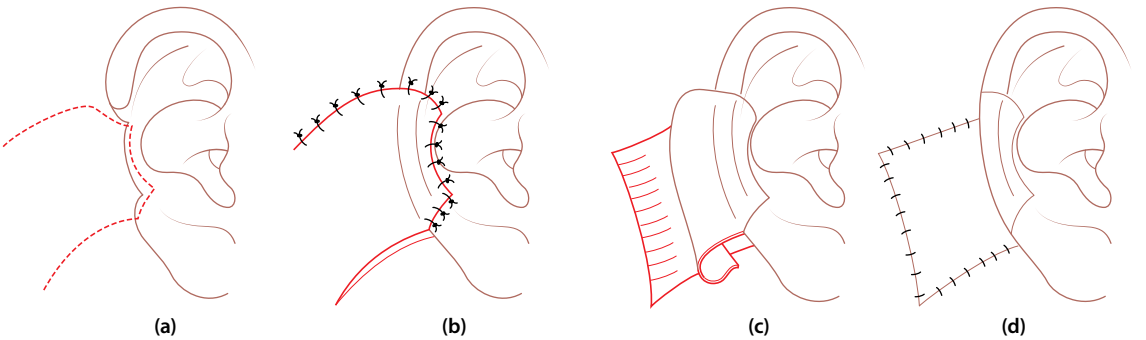

Figure 96.9 Dieffenbach postauricular flap with costal cartilage graft.

- cartilage graft in combination with a local or regional flap, e.g. Dieffenbach flap (**Figure 96.9**).

Skin-only conchal defects can be skin grafted if the perichondrium is intact. Exposed conchal cartilage may be excised to facilitate a vascular bed suitable to receive a skin graft. Due to the depressed contour of the concha, a soft bolster over the inlaid skin graft can be used to ensure adequate contact of the skin graft with the underlying soft-tissue bed. Alternatively, skin and cartilage defects of the concha may be reconstructed with a postauricular revolving-door flap.[28] It is not essential to replace the cartilage in these defects.

Lower-third ear defects include those that affect the earlobe and the antitragus. The antitragus is not a cosmetically sensitive area and isolated lesions here are uncommon. They can usually be managed by cartilage excision and direct closure or local transposition flap. The earlobe contributes significantly to the overall aesthetic appearance of the ear and defects or deformities in this area are often noticed by the patient and surrounding observers. A number of different one- and two-stage techniques utilizing local flaps have been described for earlobe reconstruction. Applying skin graft to lateral defects of the earlobe is less aesthetic and may be associated with graft contracture resulting in a persistent deformity. In order to avoid this, a cartilage batten graft sized and shaped to that of the ideal earlobe is inserted in a subcutaneous pocket deep to the flaps. Grafts used in this way are sourced from the concha, costal cartilage and nasal septum.

AUTOLOGOUS TOTAL EAR RECONSTRUCTION

The key steps for carrying out autologous total ear reconstruction are:

1. Identifying and marking the ideal site for the new ear
2. Making a 2D template and/or a 3D model for cartilage framework fabrication
3. Planning of soft-tissue cover, including skin incisions and flaps at the ideal site for the new ear
4. Costal cartilage harvest

5. Removal of remnant fibrocartilage in microtia or deformed cartilage
6. Dissection and preparation of skin and/or fascial flaps to receive cartilage framework
7. Formation of costal cartilage framework
8. Insertion of framework and inset of overlying soft tissues
9. One or more further stages of ear reconstruction, including framework elevation.

Patients are marked using the upper border of the EAM and inferior orbital margin to determine the Frankfurt horizontal as a line of reference. The upper border of the new ear is marked one ear length posterior to the most lateral point of the eyebrow on a line parallel to the Frankfurt horizontal. The lower border of the new ear should be located at the level of the upper lip, with the ear reclined posteriorly by 20 degrees along its axis.[29]

Costal cartilage for framework fabrication is harvested from the costal margin. The amount of cartilage required is estimated from the features of the template or model. Typically, three or four costal cartilages are used, including an area of synchondrosis from the 6th and 7th costal cartilages. When harvested without perichondrium, the form of the costal margin may be restored by returning diced unused cartilage into the perichondrial sleeves.[30]

Different techniques for autologous ear reconstruction are in use around the world. The most popular current techniques for microtia are those of Brent, Firmin and Nagata, and modifications of these.

The four stages of the **Brent ear reconstruction** technique are shown in **Table 96.1**.[25]

The **Nagata ear reconstruction** technique condenses the steps of the Brent technique into two stages by the utilization of local transposition flaps, with the preservation of a subcutaneous pedicle for the skin flap overlying the cavum concha of the new ear. Nagata also advocates the construction of a detailed and complex costal cartilage framework.[31] Stages of this technique are detailed in **Table 96.2** (see **Figure 96.10**).

Firmin ear reconstruction is a two-stage reconstruction technique adapted from Nagata, but which differs from Nagata in the approach to soft-tissue cover. She describes four types of skin approach for the placement of a cartilage framework in total or subtotal ear reconstruction (**Table 96.3**) and does not utilize any subcutaneous pedicles for the skin flap overlying the framework.[32] Firmin further classifies the costal cartilage framework fabricated according to the structural features that require reconstruction (**Table 96.4**).[32] Two projection pieces are added to the framework to increase the depth of the framework and accentuate the contours of the lateral surface of the new ear. 'P1' links the tragus and helical crus and provides stability to the anterior frame. 'P2' is placed under the base plate deep to the antihelix.

A comparison of the three types of costal cartilage framework is shown in **Figure 96.11**. Costal cartilage frameworks are typically carved with sculpture knives in component parts according to the templates or models and then assembled. These components, such as the helical piece, are held rigidly in place with the use of monofilament 38-gauge stainless steel wires which have high tensile strength and modulus of elasticity. This prevents displacement of the component pieces of the framework and facilitates framework vascularization and fibrous healing. The frames are made smaller than the intended size of ear reconstruction to take into account the thickness of the soft-tissue layer that is draped over it.

The cartilage framework is elevated to create ear projection and a postauricular sulcus as a separate surgical procedure 3–6 months after the frame is inserted. The ear projection produced is better maintained using a costal cartilage strut between the mastoid area and the framework in the postauricular sulcus. Vascularized soft tissue such as the temporoparietal fascial flap with an overlying split-thickness skin graft is used to sustain this cartilage strut. Alternatively, full- or split-thickness skin grafts, with or without mastoid fascial flaps, are used to reconstruct the medial (cranial) surface of the cartilage framework and postauricular sulcus. The latter technique is associated with a higher incidence of retraction of the sulcus so formed, resulting in a loss of ear projection.

TABLE 96.1 The four stages of the Brent ear reconstruction technique

Surgical stage	Description of surgical procedure
1	Carving and insertion of simple two-piece costal cartilage framework at the ideal site for the new ear
2	Ear lobule transposition and insertion of inferior framework into bivalved lobule
3	Framework elevation and full-thickness skin graft to medial surface of the new ear
4	Formation of tragus with contralateral composite conchal cartilage graft and full-thickness skin graft to concha

TABLE 96.2 The two stages of the Nagata ear reconstruction technique

Surgical stage	Description of surgical procedure
1	W-shaped skin incision with central subcutaneous pedicle for creation of neoexternal auditory meatus and local flap for the lateral surface of the earlobe
	Carving and insertion of seven-piece costal cartilage framework at the ideal site for the new ear – includes one tragal piece and two conchal pieces
2	Framework elevation supported in place with two- to four-piece costal cartilage strut
	Posteromedial surface of the new ear and cartilage strut covered with temporoparietal fascial flap and thick split-thickness skin graft

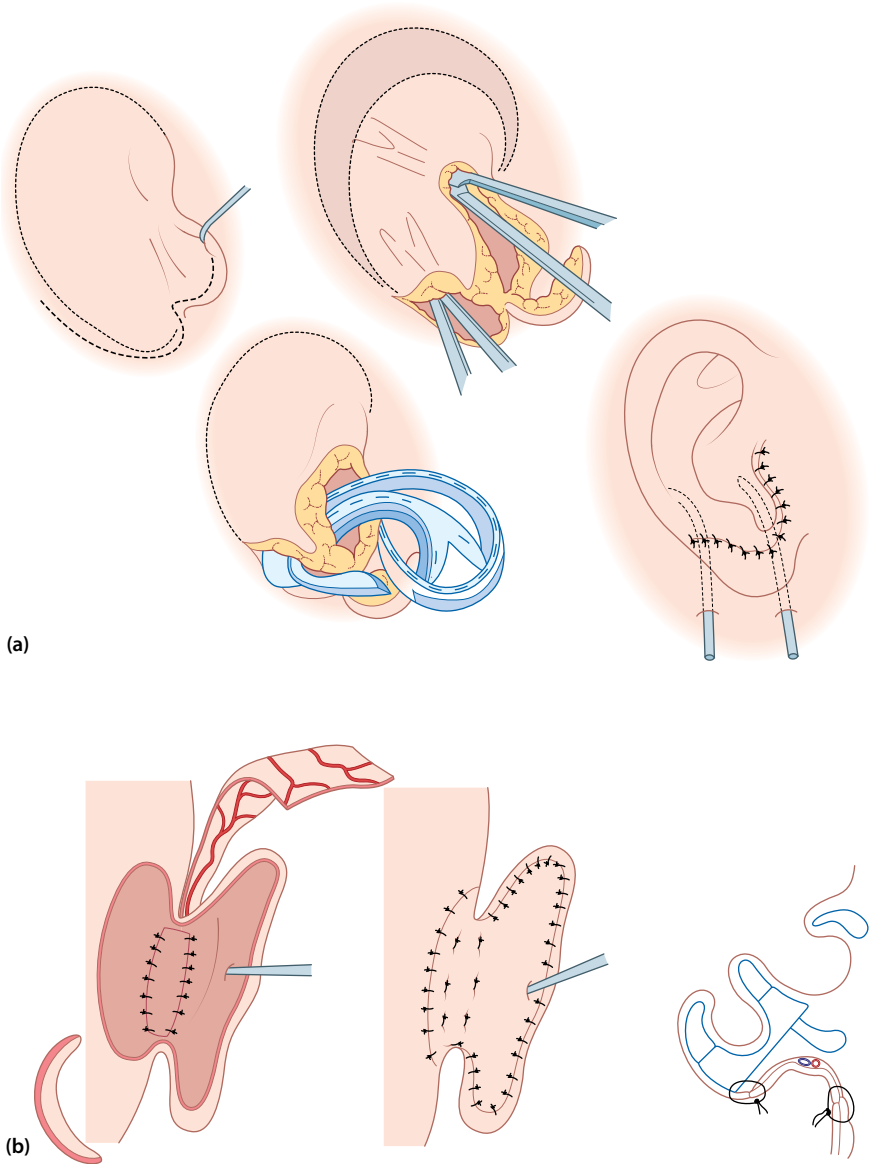

Figure 96.10 Schematic drawing of Nagata two-stage ear reconstruction procedure. (a) First stage, **(b)** second stage.

TABLE 96.3 Classification of the four types of skin approach for the placement of a cartilage framework after Firmin

Type of skin approach	Description of skin incision
1	Z-plasty skin flaps modified from Nagata
2	Transfixion skin flap, where the microtia skin envelope is released superiorly then transposed inferiorly and bivalved to accept the caudal portion of the cartilage framework
3a	Skin incision at the upper scapha of a deformed ear, where there is adequate skin cover for one-stage cover of the lateral and medial surfaces of the ear reconstruction
3b	Skin incision is placed at the anterior border of the microtia skin envelope or the mastoid hairline, where the microtia remnants are absent or not in a position to facilitate transposition or transfixion flaps

TABLE 96.4 Classification of the types of costal cartilage framework after Firmin

Type of cartilage framework	Description of framework
1	Complete framework with antitragus and tragus
2	Framework without tragus
3	Framework without antitragus and tragus

COMPLICATIONS OF EAR RECONSTRUCTION

Soft-tissue necrosis secondary to ischaemia of the covering skin and fascial flaps may occur. As a consequence, exposure of the cartilage framework may ensue that requires timely coverage with available local flaps. Infection of the cartilage framework may result from exposure and

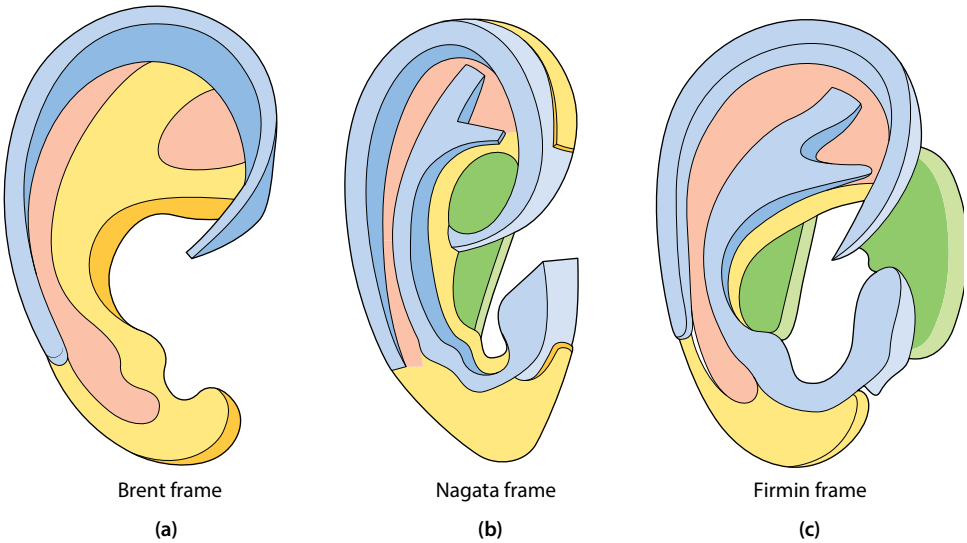

Figure 96.11 Comparison of the Brent, Nagata and Firmin costal cartilage frameworks. **(a)** The Brent framework consists of two layers of carved costal cartilage: a base plate (yellow) from which the antihelix is carved, and a separately carved helical piece (blue) which is then secured to the base plate. Note the concavity of the scapha and triangular fossa (orange) which is used to accentuate the prominence of the antihelix. **(b)** The Nagata framework is more complex and builds upon a carved base plate (yellow) with separately carved helix, antihelix (blue) and tragal (blue) structures which are secured onto the base plate with stainless steel wires. In addition, the root of the helix is anchored deep to the base plate to create depth in the concha and additional carved pieces for the cymba concha and cavum concha (green) are anchored to the underside of the base plate to enhance the 3D features of the reconstructed ear. **(c)** Firmin also uses separately carved pieces of costal cartilage to recreate the helix, antihelix and tragus (blue) on top of a base plate (yellow). However, the tragus produced is of less depth and the root of the helix is less prominent. Two other pieces of cartilage (green) are secured to the underside of the base plate and are used to create depth in the concha (P1) and anchor the positions of the helix and tragus (P2).

is a devastating complication that may require removal of the framework. Wire extrusion from the framework and alopecia along scalp incision scars may also occur. Harvest of costal cartilage grafts is associated with a small risk of pneumothorax which must be checked with a Valsalva manoeuvre before closure of the chest incision.

SUMMARY

- Successful reconstruction of a partial ear defect demands meticulous analysis of the deficit and knowledge of key structural features which would benefit from cartilage replacement.
- Aesthetically pleasing partial ear reconstruction is based upon a sound understanding of the donor sources for cartilage replacement and the available options (based on vascular anatomy) for local skin and fascial flaps.
- Surgeons intending to perform subtotal or total ear reconstruction need to be attentive to details throughout the planning process, including the intended proportions of the new ear.
- Careful consideration should be paid to the formation of an anatomically accurate framework and the design of surgical incisions for local flaps used to protect and sustain it.
- In order to ensure familiarity and competence with the equipment required for autologous ear reconstruction (e.g. stainless steel wires and sculpture knives) and with the handling of the costal cartilage graft used, it is recommended that a period of training is undertaken.

BEST CLINICAL PRACTICE

- ✓ Acquire the appropriate training and expertise.
- ✓ Ideally, work within a multidisciplinary team able to offer the option of prosthetic reconstruction and psychological support.
- ✓ Audit your results.

FUTURE RESEARCH

There is poor quality of evidence available for partial and total ear reconstruction techniques. This is because of the myriad different techniques which have been published, often to address the variable types of partial defects and congenital ear anomalies presenting to the ear reconstruction surgeon. In addition, international standardized outcome measures for surgery are absent, making it difficult to run surgical trials. Further research should involve the development of and consensus for international outcome measures. Subsequent case series using a consistent technique and reporting these outcomes will allow comparison between techniques and centres of excellence.

KEY POINTS

- Intimate knowledge of the anatomy, features and location of the ear is essential for the ear reconstruction surgeon.
- Ear reconstruction is best performed with the support of a multidisciplinary team.
- Partial ear reconstruction should take into account the aesthetic significance of the area to be reconstructed and whether structural support is required for reconstruction.
- Surgery for autologous total ear reconstruction is technically demanding and usually performed in stages.
- An anatomically accurate costal cartilage framework providing structural support and overlying vascularized soft-tissue cover is essential for autologous total ear reconstruction.

ACKNOWLEDGEMENTS

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CHAPTER 97

A COMBINED PROSTHETIC AND SURGICAL APPROACH

Hitesh Koria, M. Stephen Dover and Steve Worrollo

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SEARCH STRATEGY

The references in this chapter are supported by a Medline search and a manual search of maxillofacial technical journals using the key words/phrases facial prostheses, maxillofacial prosthetics, rehabilitation, facial defect, prosthesis and implants and extra-oral implants.

INTRODUCTION

In our increasingly body-conscious society, there is a stigma attached to disfigurement. Acquired facial defects, especially after radical surgical operations, very often result in huge functional, cosmetic and psychological deformity in patients.[1] Complex prosthetic rehabilitation, such as the midface, is necessary as alternative treatment when facial defects cannot be surgically fulfilled.

A team consisting of maxillofacial surgeons, plastic surgeons and restorative dentists play an important part for the success of the final outcomes. Surgical reconstruction of these defects is frequently limited due to unfavourable conditions, such as vascularity following radiotherapy and insufficient residual soft and hard tissues.

Facial prosthesis using dental implants and bars or magnets are the preferred choice of retention methods in the replacement of missing hard and soft facial tissues. Nose, eye and ear form, colouration and texture must be as unnoticeable from the surrounding natural tissues as possible. Rehabilitation efforts can be successful only when patients can appear in public without fear of attracting unwanted attention.

The quality of life of patients with severe deformity or even head and neck cancer patients prior to maxillofacial prosthetic rehabilitation can be low, but little or no evidence is currently available to assess the impact facial prosthetics can have following surgery.

HISTORY

The use of prosthetics has been well documented throughout history. The use of facial prostheses was first reported in ancient Egypt. Evidence documented historically comes from the 16th century,[2] when a French surgeon Ambroise Paré described the first nose prostheses from gold, silver and 'papier mâché', which were held to the face by a string tied around the back of the head.[2]

It was not until the beginning of the 19th century that successful nasal reconstruction was reported in India[3] and only at the end of the 19th century did plastic surgery begin to provide an alternative to facial prosthetics.

In the 20th century, while the quality of realistic craniofacial prostheses was considerably improved with the introduction of silicone materials and greater expectations from patients, the problem of their retention, which is important for aesthetics, function and comfort, was not entirely solved.[4]

Prostheses were used for defects which could not be surgically reconstructed or for patients whose treatment was delayed. Teams of surgeons, working together with dentists,

helped develop new techniques that radically improved the outcome for patients – an early example of multidisciplinary teams, which are now more common in modern-day practice – hence the importance of being treated in a regional centre with specialized surgeons, whether it be for craniofacial, oncological or traumatic rehabilitation.[3]

PATIENT SELECTION

Defects in the craniofacial region can improve the final outcome for patients with facial disfigurement. Careful planning of surgical resections and careful handling of the traumatic defects can influence long-term rehabilitation. The decision to provide a patient with a facial prosthesis should always be carefully evaluated and there are many factors to consider.

Prosthetics should be used to complement reconstructive surgery. The decision to use prostheses rather than autologous materials should be made only after considering all available options. The aetiology of defects is important in deciding the type of treatment and timing of any reconstructive procedures.

The following factors should be considered when planning treatment with facial prosthetics:

- **medical factors** – the patient's physiological status and general health
- **patient factors** – age, dexterity, hygiene, motivation, compliance
- **defect considerations** – use of autogenous tissue, soft-tissue cover, skin condition, defect shape to allow optimum prostheses positioning, availability of bone for implant placement, support for prostheses, facial movement during function, previous radiotherapy.

USE OF IMPLANTS IN PROSTHETICS

Facial

It was Brånemark who first placed a modified extraoral implant for a bone-anchored hearing aid (BAHA) in 1977 and for a bone-anchored auricular prosthesis in 1979.[5]

The benefits of implant-retained prostheses have been recognized for many years and have changed the concepts of maxillofacial prosthetic rehabilitation. Osseointegrated implants are widely used for the retention of orbital, auricular and nasal prostheses. Extraoral implants (3 mm or 4 mm) should generally be used in auricular defects, as the bone in that area is fairly thin, and dental implants used for orbital and nasal defects due to the length of the implant.

Their use reduces the need for adhesives and any related problems such as discolouration and deterioration of the prosthetic material. Osseointegration has allowed predictable retention of prostheses. However, it is not suitable or desirable for all patients and on its own will not guarantee an acceptable aesthetic result. All prosthetic and surgical options need to be evaluated by the team, including the patient, to achieve optimum results.

Osseointegrated implants have various advantages over either adhesive or spectacle-retained prostheses for the reconstruction of facial defects. They provide better retention, so that the prosthesis is properly positioned and the patient can wear it more confidently. There is no skin irritation from adhesive and the prosthesis does not need to have adhesive cleaned off each time it is used, which increases the deterioration of the materials used. The edges of the prosthesis can be made thinner and feathered, blending better into the skin, which offers the patient enhanced aesthetics.

A pre-operative planning meeting with the patient and multidisciplinary team provides the opportunity not only to consider different prosthetic options but also for the patient to ask the prosthetist questions about aftercare, such as cleaning of the abutments and prosthesis. Development and application of osseointegrated implants to facial defects has, in part, changed patient perceptions of facial prosthetics. Implants allow convenient and secure positioning of the prosthesis, leading to greater patient acceptance. Patients like the security, comfort and convenience of implant-retained prostheses, benefits that are not attainable with earlier methods of retention. Surgeons have come to appreciate the reduced need for numerous complex surgical reconstructive procedures in many of these patients.

For large defects, a multidisciplinary approach is recommended, combining flap reconstruction and implant-retained prosthetic rehabilitation to achieve optimal results.

Although implants are the 'gold standard' for rehabilitation, earlier reports have shown that implants are not uniformly successful and the failure rates in some patients/sites are quite high.[4] The failures and complications appear to be site-specific and radiation- and time-dependent, although implants have been used successfully in patients who have had vascularized and non-vascularized bone and soft-tissue grafts to the jaws and facial skeleton.

It has been suggested that careful selection of patients and pre-surgical planning are necessary to achieve predictable outcomes when using primary placement, and close teamwork between oncological surgeons and the maxillofacial prosthetics department is vital.[6]

Midfacial

Midface defects can be divided into two major categories:

- **midface defects**, which include the nose and/or the upper lip
- **lateral defects**, which include the cheek and the orbital contents.

The choice between surgical reconstruction and prosthetic rehabilitation of large facial defects remains a difficult one and depends on the size and aetiology of the defect, as well as on the wishes of the patient. The aims of surgical and prosthetic rehabilitation are for the replacement of missing soft and hard facial structures while giving patients

TABLE 97.1 Comparison of surgical and prosthetic rehabilitation

Rehabilitation	Advantages	Disadvantages
Surgical	Uses patient's own tissue Reconstruction at same time as resection may be possible More acceptable to patient Does not require prosthetic maintenance/ replacements	No visual access for inspection of defect site (for tumour patients) May require multiple procedures Variable aesthetic result: depends on quality of host site Separate donor site often required
Prosthetic	Immediate temporary reconstruction Inspection of defect (tumour patients) Predictable results Easily modifiable Does not preclude future surgical reconstruction Immediate temporary reconstruction	Non-mobile tissue Requires skilled prosthetist Long-term follow-up required Replacement prosthesis required

a better quality of life along with social acceptance. **Table 97.1** summarizes the advantages and disadvantages of surgical and prosthetic rehabilitation.

The use of osseointegration in the midface region can dramatically improve anchorage and enable complex and movable connections to be accommodated within the prostheses.[7]

Placing fixtures at the time of ablative surgery gives great advantages. It significantly reduces the time before prosthetic rehabilitation can commence. Fixtures are placed in bone prior to any radiotherapy, in so doing increasing implant osseointegration and survival rate. Implants are best placed in areas where bone quality has not been compromised and still has a good thickness available. It is often necessary to trim back thin bone to allow placement into thicker denser bone. Intraoral fixtures should always be used to take advantage of as much depth of bone in the premaxilla as possible. It can be advantageous to utilize zygomatic implants which use good quality bone at distant sites.[8] Patients will also generally see the prosthetist as early as possible so that impressions can be taken of the facial structures prior to ablative surgery. This enables a template to be constructed for use as a starting point in reconstructive planning of the lost tissues.

AETIOLOGY OF FACIAL DEFECTS

The diagnoses which are indicated for surgical treatment are divided into three main categories:

- congenital
- trauma
- disease

} acquired

Congenital defects

Congenital defects include the absence of:

- the ear (microtia)
- the nose (arhina)
- the eye and orbits (anoptholima).

In patients with congenital defects, treatment is an elected decision which can only be made by the patient when provided with all the relevant information and the ability to meet and talk to patients previously treated. This gives a balanced, informed view of potential treatment options. It is, of course, possible that the patient may accept the defect, or is unwilling to undergo any possible treatment.

Acquired defects

Acquired traumatic defects include those caused by:

- road traffic accidents
- thermal injuries
- ballistic injuries
- accidental injury
- physical assault.

Acquired surgical defects can be created by removal of benign and malignant tumours. Patients with acquired defects have to come to terms with a sudden change of appearance. Cancer patients will also have the psychological worry of dealing with potential life-threatening conditions, for which the treatment can involve the loss of vital structures and create potential impairment of function, such as sight, hearing, swallowing, speech, taste and smell. Every effort should be made to use the patient's own tissue and, if necessary, surgical procedures are undertaken in stages until the optimum result is obtained. If surgery is not possible (or will involve multiple procedures with an unpredictable result), prosthetics can be considered.

For patients with tumours, the defect size is determined by the amount of tissue that has to be removed during ablative resection. How the defect is left is of paramount importance if a prosthetic is to be used as it will determine the final aesthetic result. Ideally, thin skin cover is always preferable as this allows for an optimum interface between defect and prosthesis. Bulky flaps are to be avoided as they restrict contouring and positioning of prostheses and will not allow mirror imaging of existing structures.

Defect reconstruction

The reconstruction of hard and soft tissues is a combination of medicine and art. Major defects in the craniofacial region have challenged the skills of the reconstructive surgeon. The use of microvascular free-flap transfers of

hard and soft tissue in the mandible, maxilla, cranial and midface regions has greatly improved the outcome for patients. Surgical techniques have advanced using autogenous tissues to replace aesthetically difficult areas, such as the nose and pinna.

There may also be the case where a decision not to reconstruct is made. This allows the clinician to look for evidence of any recurrent disease at the defect site, prior to any secondary reconstruction. Alternatively, the defect may be obliterated with a large, bulky flap to close a large surgical cavity. This can have the advantage of creating an oral–nasal seal to allow patients to talk and eat/swallow without problems but a disadvantage is that it has limited or unacceptable aesthetics.

Craniofacial defects should be reconstructed as soon as the patient's condition allows. This is an important factor for all patients, including those with poor prognosis. With the high standard of autogenous and prosthetic techniques available, it is not acceptable for patients with facial deformity to be precluded from as normal a life as possible.

Small soft-tissue defects are reconstructed by covering with skin grafts, deeper defects by the use of local flaps, with larger defects which usually requiring coverage by free flaps. Bony defects are mainly reconstructed by non-vascularized bone graft, provided there is sufficient soft-tissue coverage in non-irradiated tissue. For defects of both hard and soft tissue, a composite flap containing bone and skin is often used. Skeletal fixation is obtained by use of plates and screws. Sites of composite free flaps include iliac crest, fibula, scapula and radius. Radial forearm flaps have a large surface area of skin to volume; this makes them thin and suitable for both intra- and extraoral mucosal or skin defects. The use of bulky flaps can compromise aesthetics and make prosthetic options impracticable. Smaller, thinner flaps and skin grafting may give coverage without compromising prosthetic possibilities.

TREATMENT USING DIGITAL APPLICATIONS

There have been many developments in materials used for the production of prostheses. The advent of percutaneous osseointegrated implants has dramatically improved the potential for retention of a prosthesis. However, many of the construction methods and mould-making have changed, becoming highly skilled and time-consuming. Each prosthesis is individual and the use of high technology has been difficult to adapt or is not cost-effective in some individual cases.

With advances in software applications (manipulation and design) using computed tomography (CT) data, there are programs available which allow 3D simulation of facial reconstructive methods including osteotomy and distraction procedures. Data from medical scanners (CT, magnetic resonance imaging (MRI)) can be used to reproduce physical models of human anatomy via additive layer manufacture (ALM) or rapid prototyping (RP).

Several techniques exist, the most common being stereolithography. The basic principle of creating a 3D structure is to build an object in layers using the CT data and an optical scanning system that deposits a polymeric resin material to mirror the object on screen one layer at a time onto the 'build bed' until the desired object is completed. Each layer of resin is cured using a high-intensity UV light, ensuring the strength of the model.

It is possible to have individual implant templates for either soft tissue or direct bone contact to allow exact implant placement. Precise anatomical models (3D) made by ALM/RP enable surgeons to view and evaluate their treatment plans. On this physical model, osteotomy lines or drilling holes can be indicated and trial surgery can be undertaken. These models are also used for reconstructive procedures. 3D models act as visual aids for the surgical team, indicating the resection lines and allowing the prosthetics team to pre-bend the reconstruction plates. This allows accurate positioning and fixation of the bony flap in the planned location. The applications of these models can be advantageous in facial reconstruction, the production of obturator prostheses for maxillary defects and designing and planning cranioplasties for skull defects.

Improvements in surgical techniques and the advent of specialization have enabled more accurate and aesthetic reconstructions to be performed. While prosthetic materials continue to be improved and refined, these surgical improvements may render a prosthesis necessary in a more limited format. The necessity of treating tumours by ablative surgery in the future may be reduced by other treatment regimes and therefore the necessity to surgically or prosthetically reconstruct these defects could be reduced.

The use of high-technology and digital imaging in processing complex shapes and patterns is now achievable and readily available. In certain circumstances it can produce moulds and patterns that are difficult to duplicate by conventional methods. It remains to be seen whether the use of advanced technology is cost-effective in individual cases or is just another method of obtaining the same result. As with most new techniques, there is a tendency for overuse, and careful evaluation of each individual case should be balanced to obtain the optimum result and cost-effectiveness of the process. However, it is now an essential and welcome addition to the practice of reconstructive surgical and prosthetic techniques.

TREATMENT PROTOCOL

The treatment of a patient with facial or oral cancer or after disfiguring trauma is a collaborative team effort. Free-tissue transfers are habitually used to reconstruct both the soft tissue and bone defect instantly following the ablative surgery. A selected proportion of patients receive radiation 4–6 weeks post-operatively. The type of radiation therapy prescribed by a radiation oncologist depends on many factors, including:

- type of cancer
- size of the cancer
- location of the cancer

- pathological status, i.e. margins, nodal involvement
- how close the cancer is to normal tissues that are sensitive to radiation
- how far into the body the radiation needs to travel
- the patient's general health and medical history
- whether the patient will have other types of cancer treatment
- other factors, e.g. the patient's age and other medical conditions.

The total radiation dose to the tumour bed depends on the presence or absence of microscopic disease at the surgical margin. Radiation positioners are used extensively, and radiation fields are configured to minimize exposure of the major salivary glands to high doses of irradiation. Radiation dose to bone can often be minimized in areas of proposed implant sites.

As a generalization, 6 weeks after ablative surgery patients would receive radiation therapy for 5–7 weeks. Prostheses are generally made as soon as the healing from reconstructive surgery and radiotherapy permit. Whether implants are inserted at the primary stage of surgery may depend on the need for post-operative radiation therapy. At least three intraoral implants of 7–15 mm in length and 3.75 mm in diameter (orbits and nasal defects) would give adequate retention. Ideal placement of the implants depends upon the skill of the surgeon and, where possible, the prosthetist would advise to achieve the best prosthetic outcome.

DEFECT SITES

Nasal

Nasal defects are predominately as a result of tumour surgery or traumatic loss; congenital absence is an extremely rare condition. The goal of reconstruction is to construct an aesthetically pleasing and 'functional' nose. Autogenous reconstruction must address the underlying cartilaginous support, cutaneous coverage and reconstruction of nasal lining.

Acquired defects produce a variety of midface deformities dependent on the extent of traumatic injury or ablative resection. Smaller defects are easier to reconstruct using autogenous methods. The cosmetic anatomy of the nose is classified in five aesthetic units: dorsum, lateral tip, tip, alar lobule and soft-tissue triangle, as described by Burget and Menick.[9]

The majority of acquired defects are confined to skin. Skin grafts from the postauricular or preauricular area are ideal because of colour and texture match in the proximal two-thirds of the nose. The distal tip requires 'thicker' coverage and is usually best reconstructed with a composite flap.

The decision to reconstruct is dependent on the health of the patient, the quality and availability of donor tissue, the presence of any residual disease and patient choice. The defect may also involve orbital and maxillectomy components, and this should be considered in treatment planning.

If the lip is to be sacrificed, it is essential to reconstruct the competent boundaries if possible. This can be achieved by using nasolabial or free flaps.[10] Prosthetic reconstruction is difficult in these cases because of the mobility of surrounding tissue and the functional seal required for lip competence. Large prostheses can be difficult to stabilize and retain.

Orbital or ocular

Any defect that is confined to the globe is treated with an 'indwelling prosthesis', which sits behind the lids. These prostheses, which are self-retaining, have historically been referred to as 'glass eyes', although in the UK they are now always made in acrylic. Defects including the loss of orbital contents and the lids are more extensive and an orbital prosthesis will often be the treatment of choice.

The loss or absence of an eye may be caused by a congenital defect, irreparable trauma, tumour, a painful blind eye, sympathetic ophthalmia, or the need for histological confirmation of a suspected diagnosis. Orbital diseases are relatively rare but, considering the anatomy of surrounding structures, they present a very serious disorder. Depending on the severity of the situation, the surgical management may include one of three approaches: evisceration, enucleation or exenteration. The majority of patients requiring orbital prostheses have acquired defects as a result of tumour surgery. These can also include defects into the maxilla and or nasal area. There are three types of surgery for which prosthetics are required (**Table 97.2**):

- **Evisceration** is a surgical procedure wherein the intraocular contents of the globe are removed, leaving the sclera, Tenon's capsule, conjunctiva, extraocular muscles and optic nerve undisturbed; the cornea may be retained or excised.
- **Enucleation** is the surgical removal of the globe and a portion of the optic nerve from the orbit.
- **Orbital exenteration** is the removal of the entire orbit, usually involving partial or total removal of the eyelids, and is primarily performed in order to eradicate a malignant orbital tumour.

Specific diagnostics is provided by an ocularist; otorhinolaryngologist and dentist examinations are also suitable. Auxiliary imaging methods are also an indispensable part of the diagnostic procedure. These include X-ray images of the skull in dorsoventral, semiaxial and lateral projection. Ultrasonography, CT and nuclear MRI are also frequently employed. According to the specific diagnosis it is possible

TABLE 97.2 Orbital surgery requiring prostheses

Term	Tissue lost	Solution
Evisceration	Cornea	Hepatic/cosmetic shell
Enucleation	Eye	Artificial eye
Exenteration	Eye and orbital contents	Orbital prostheses

to establish precisely the extent of the damage to the eye and surrounding structures in the orbital area and to determine a medical treatment. In the treatment of solid tumours, radical surgery is usually the first step despite the risk of possible functional and aesthetic defects.

The disfigurement associated with the loss of an eye can cause significant physical and emotional problems. Replacement of the lost eye as soon as possible after healing is necessary to promote physical and psychological healing for the patient and to improve social acceptance.

Prosthetic rehabilitation that restores these facial disfigurements may improve the level of function and self-esteem for patients. However, difficulties with facial prostheses arise due to movable tissue beds, quality of prosthesis retention and associated skin reactions to adhesives. The use of osseointegrated implants in the craniofacial region reduces prosthesis limitations associated with medical-grade adhesives and is a treatment option with high long-term success rates.

Facial prosthesis with three dental implants is a method of choice in the replacement of missing hard and soft orofacial tissues. Prosthesis form, colouration and texture must be as indiscernible from the surrounding natural tissues as possible. Rehabilitation efforts can only be successful when patients can appear in public without fear of attracting unwanted attention. Dental implant support gives the patient confidence in society. An important requirement for successful treatment of such handicapped patients is high-quality osseous tissue of defect margins.

Auricular

The indications for an autogenous auricular versus prosthetic auricular reconstruction with osseointegrated implant-retained prostheses were outlined in literature. The choice between the two techniques depends more on the surgeon's training and tradition than on an analysis of which procedure is preferable in a given clinical situation. For example, most children with microtia in the USA are treated with autogenous techniques. In contrast, the same deformities in the UK are more commonly treated with prosthetics. Patients with post-traumatic or post-ablative auricular defects are more often adults and their defects differ from those of children with congenital deformities in several ways. First, the skin loss and scarring resulting from trauma or previous surgery may make standard autogenous reconstruction difficult. Second, the tragus is frequently preserved in the trauma/ablative patient, making the aesthetics of prosthetic reconstruction much more favourable. The presence of a tragus allows the anterior border of the prosthesis to be hidden, which is a major aesthetic benefit.

The incidence of malformation of the external ear is around 1 : 10 000 live births.[11] Auricular defects frequently appear in combination with those of the external auditory canal and middle ear. Unilateral microtia may be associated with facial malformations involving the first and second branchial arch. Unilateral or bilateral microtia can be part of a bilateral condition, such as mandibular facial disostosis (Treacher Collins syndrome).

Children born with congenital defects can invoke feelings of anxiety and guilt, causing the parents to seek an immediate solution. This should be resisted and reassurance should be given to parents with an explanation of potential treatments available. Delay in treatment will allow sufficient growth to occur for an optimum aesthetic result to be achieved and for the child to understand and be involved in the process.[5]

The introduction of parents to other parents of children with the same condition is very useful in allaying fears that their child was the only one with this condition. Patients are best assessed by a multidisciplinary team, which should include specialists in ENT, maxillofacial, prosthetics and plastic surgery. Depending on the severity of the condition, a variety of treatment options may need to be considered.

The importance of hearing to development should never be overlooked or considered less important than aesthetics. It should be treated as a priority and, if necessary, a BAHA should precede ear reconstruction.

A realistic age for successful prosthetics in children is upward of 10–12 years. Our experience is that, before this age, children are not sufficiently developed physically or psychologically to commit to a long-term treatment regime.

Many patients referred for prosthetics have had disappointing autogenous reconstructions. This should not be used as a reason to prevent this option to be explored further, as cooperation between prosthetics and autogenous reconstruction is vital to achieve a balanced and appropriate treatment for the varied range of patients with auricular defects.[12] There have been great improvements in autogenous reconstructive techniques with major contributions by Brent and Nagata.[13, 14] With improved techniques, more consistent aesthetic results can be achieved, but specialization is as important as technique to achieve these standards. The decision to go for the prosthetic option is easier when an autogenous reconstruction is totally impractical, such as the presence of compromised skin or following tumour resection.

Indications for auricular prostheses include:

- lack of autogenous tissue
- irradiated area
- failed autogenous reconstruction
- cancer resection
- absence of the lower half of the pinna
- microtia
- patient preference
- craniofacial anomaly
- traumatic defect.

Microtia cases can predictably be reconstructed with a prosthesis, but they have the disadvantage of long-term follow-up, and treatment can compromise any future autogenous reconstruction by removal of ear remnants or compromise available soft tissue. The amount of ear left (particularly the lower third) or the position and shape of remnants can make autogenous reconstruction a more viable option. There is a role for both options

in auricular reconstruction and the combination of both autogenous and prosthetic options working to complement each other can only benefit patient treatment regimes.

Once treatment is decided upon, careful planning is required to determine the stages and timing of treatment. The prosthetist should be involved in all stages of treatment if prosthetics is the chosen option.

The auricular region was found to be the most dependable implant site. Patients having implants placed for this defect will possibly benefit from having CT scans. This allows for evaluation of the proposed bone sites in an attempt to maximize implant length. The mastoid air cells frequently pose logistical problems at the most inferior auricular implant sites, and occasionally implant position has to be recalculated. Exposure of the air cells at the time of implant placement does not appear to cause any detrimental effects. If there is adequate bone to provide stability, the implant may be left in position; otherwise, a new site will have to be found. The use of two implants in the auricular region reduces the amount of cantilevering and prevents any rotation of the prosthesis, conferring mechanical advantage. All implants are connected with a gold bar which sits above the skin, and retention is achieved with gold clips. Alternative methods can be used, including magnets and/or adhesives.

Oral cavity

Intraoral prosthetics are well documented in technical and dental literature. This section will only cover prosthetics in relation to ablative surgery.

The management of oral cancer requires understanding and skills in assessment, access and ablative and reconstructive surgery. Prosthetic input may be required in dealing with complex and difficult defects. Removal of soft and hard tissue has a dramatic effect on function; small defects can be closed by local flaps, with free-tissue transfer available for larger defects. While surgical reconstruction has improved and is the treatment of choice, there are occasions when prosthetics is a suitable option or if a surgical reconstruction has failed.

The objective of prosthetic rehabilitation in patients with defects of the orofacial region is the restoration of form, function and appearance. In patients with orofacial cancer, a decision should be made as to whether immediate or staged surgical reconstruction is advocated. If possible, a one-stage procedure should be used. Surgery involving the oral cavity will require pre-operative dental checks and any necessary treatment should be undertaken prior to surgery. When a maxillary resection requires an intermediate obturator, impressions are required pre-operatively to enable design and construction of the plate.

The design needs to consider how the plate is to be retained, the approximate extent of the resection and whether any teeth are to be lost or utilized for retention. The type of dressing/pack is important as the type of pack can affect the design of the plate.

In the maxilla, the bony margins and alveolus should be trimmed parallel. The hard palate pterygoid plates and nasal septum should be examined and cut back to provide a smooth, non-sharp surface and, where possible, covered with local mucosa.

Following a maxillectomy, it is important to remove the coronoid process of the mandible as it can dislodge and break the seal of a definite prosthesis.

The surgical plate is essential to immediately restore speech and mastication and to provide support for soft tissue. It must be possible to modify any prostheses at the time of surgery to accommodate any surgical variations that may be necessary.

The obturator is retained by using skeletal wiring or bone screws through the acrylic plate or by clasping to existing teeth. It is possible to use pourable, expandable silastic foam both as a dressing medium and to provide retention by a mechanical attachment to the plate.[5] This technique requires the dental plate to be held in place and the foam is poured or syringed into the defect from above the plate. The foam will expand to fill the defect and connect with the retentive posts that are incorporated into the underside of the plate. The foam can easily be trimmed with scissors to give a flexible and very accurate fitting 'bung' which obturates the defect and provides support and retention to the plate. It is useful to pour a duplicate foam which can be used in the maxillofacial laboratory to replicate further foams which can be used during the healing phase. With practice and help, the patient can quickly learn to remove the plate and separate the foam component for cleaning. This can be performed until the healing is complete and a definitive prosthesis can be provided. The foam is particularly useful during any radiotherapy treatment as its flexibility makes it easy to fit and it is well tolerated by sensitive tissue.

STAGES IN PROSTHETIC CONSTRUCTION

Various technical stages are involved in the fabrication of prostheses (**Figure 97.1**):

- impression
- pattern
- mould
- processing
- fitting.

These include taking an impression of the defect to create a master cast on which a wax pattern is sculpted. This can be adjusted and aligned on the patient to achieve the desired contour and orientation.

When completed, a two- or three-part mould is constructed and, using the lost wax technique, a void is created which is then replaced by the prosthetic material. The materials of choice are silicone elastomers, which are individually coloured to match patient skin shades.

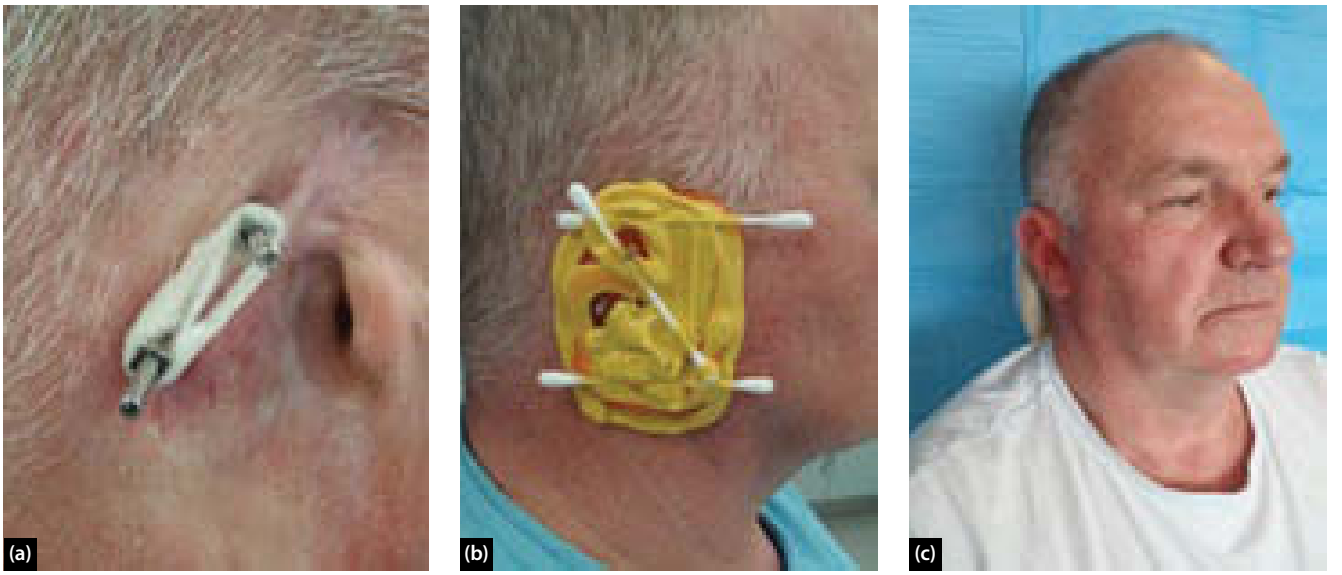


Figure 97.1 Prosthesis construction. (a,b) Impression stage for the fabrication for an ear prosthesis. **(b)** Cotton buds are used to determine the highest and lowest point of the ear to match the opposing side. **(c)** Wax trial of the ear to determine the final position and fit.

FACIAL PROSTHESIS RETENTION METHODS

The success of facial prostheses depends not just on aesthetics but on the retentive qualities. It must be comfortable and give confidence to the wearer. Methods of retention are:

- adhesive
- mechanical/anatomical
- implant.

With some prosthetic devices, retention can be retained by virtue of its anatomical location, for example an artificial eye held in place by the eyelids. This also disguises any margins.

Adhesive

Until the advent of implants, adhesives were often the method of choice for extraoral prostheses, providing good aesthetics if used carefully by a compliant patient. The adhesives used are waterproof and, if correctly applied, the prostheses will remain in position for many hours. Most problems are encountered by the continual fitting and removal of the prostheses. This can have a detrimental effect, particularly on the fine edges of the prostheses. Patients will need a certain amount of dexterity to be able to locate and position the prostheses. The type and quality of the skin can influence the choice of adhesive and the suitability of this technique. Patients with broken or compromised skin are best treated with other retentive methods.

Mechanical/anatomical

Using mechanical retention of facial prostheses is the oldest form of retention. Early retention included spring bands and straps. Current facial prosthetic mechanical methods are generally limited to the use of spectacle frames. Mechanical retention can be incorporated into interlocking intra- and extraoral prosthetic combinations, such as an obturator linked to an orbital prosthesis. Spectacle-retained prostheses are still useful in cases where simplicity and ease of location are of paramount importance. They have a particular application in the elderly and patients who have dexterity problems. The prosthesis is attached to the spectacle frame, which means that the patient is not able to remove their glasses without revealing the defect.

The adjustment of the glasses is important as it will have a direct bearing on the location and fit of the prostheses. Anatomical retention is possible in patients who have favourable undercut tissue areas; soft silicone flanges may be incorporated within a prosthesis to engage these areas.

Obtaining the correct amount of retentive pressure is difficult and care must be exercised not to ulcerate the tissue. This technique is more suited to intraoral defects as obturator-retention extraoral prostheses are more likely to be affected by facial movements, which can cause the loss of margin integrity.

Implant retained

The use of implants provides a stable and secure method of retention which allows very thin prosthesis margins for maximum aesthetics. Used first extraorally in Sweden in 1977, it is an established technique that provides predictable results for patients with various craniofacial defects.[15, 16] Implants allow prostheses to be extremely stable and secure. The prosthesis is generally retained in place by a rigid bar with clips or by magnets incorporated in the prosthesis connecting to magnetic caps on the implant.[17]

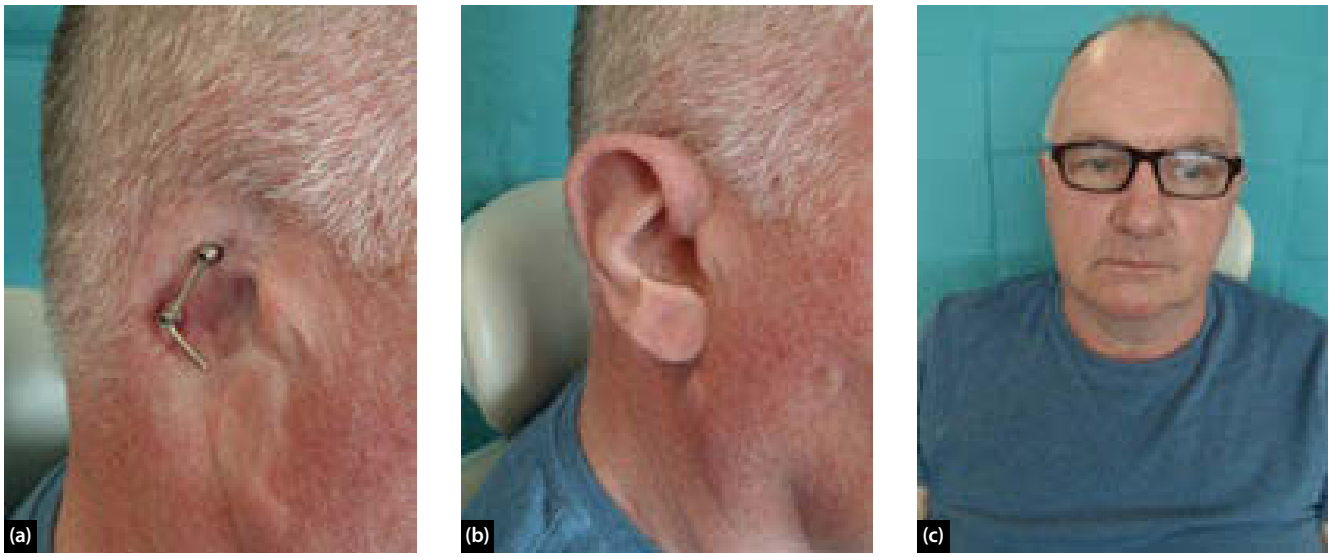


Figure 97.2 Prosthesis retention. (a) Bar design for retention using the bar and clip method. **(b,c)** Finished results.

The number of implants required for retention of the prosthesis is determined by the size and shape of the defect. Auricular defects that involve only the pinna will usually require two implants for adequate retention. This is achieved by a bar splint and clip arrangement (**Figure 97.2**). In cases where bone quality is poor or when tissue is irradiated, it is advisable to place further fixtures as 'sleepers' in case of future failures.

Following fixture placement, the skin-penetrating abutment height and type are determined by the thickness of the tissue and the aesthetic requirements. It can be advisable to place healing abutments initially and then the prosthetist can select the optimum abutment type and size following the healing phase. The abutments are fitted with the appropriate prosthetic components, depending on the retention elements selected for prosthesis attachment. If necessary, angled abutments can be used to aid prosthesis location. In certain cases, prosthetic components can be connected directly to the fixture.

The bar and clip arrangement has the advantage that the clips are adjustable and the bar design can be modified to keep retention components low within the prosthesis. The bar is connected by gold screws into the abutments (**Figure 97.2a**).

Magnets have a role with some patients in auricular cases and retention can be further enhanced by using lip magnets, which have increased resistance to lateral dislodgement. Magnets are particularly useful in orbital and midface cases where bar construction is difficult or complex and location of the prosthesis could be difficult for the patient.

AFTERCARE/PATIENT MANAGEMENT

The choice of prosthetic reconstruction is an ongoing commitment by the prosthetic team and the patient. The patient has to maintain hygiene of the area, particularly if there are skin-penetrating abutments. They have to exercise care in positioning and cleaning the prosthesis and attend for long-term follow-up.

The success of the prosthesis depends on the ability of the prosthetist to design a functional and well-fitting prosthesis. The prosthetist should give instructions on how to position, apply and remove prostheses with any necessary details regarding wearing. It is important that the prosthesis does not restrict the patient's activities and lifestyle. Implant-borne prostheses give the most predictable results but should not be considered the only option.

Dealing with patients with facial disfigurement is very demanding and requires an understanding of patient expectations as well as of what is practical or possible.[18] Patient reactions to facial disfigurement vary greatly. Time spent with patients in consultation is important in building a relationship to enable sensible and practical options to be considered.

Quality-of-life outcomes are now a welcome and vital issue to be considered in patient management.[19] Patients will require lifelong follow-up for maintenance and adjustment of the prostheses, the skin fitting area and implant and abutments in osseointegration cases.[20] The commitment to long-term management must be discussed with the patient.

CASE STUDIES

We would like to thank Mr Nicholas White, Consultant Plastic and Craniofacial Surgeon, University Hospital Birmingham NHS Foundation Trust, for the use of his patients as case studies.

Case study 1

PRESENTATION

In 2011 a 58-year-old female presented with large cylindromas to the scalp, face and ears which had invaded underlying structures (**Figure 97.3**).

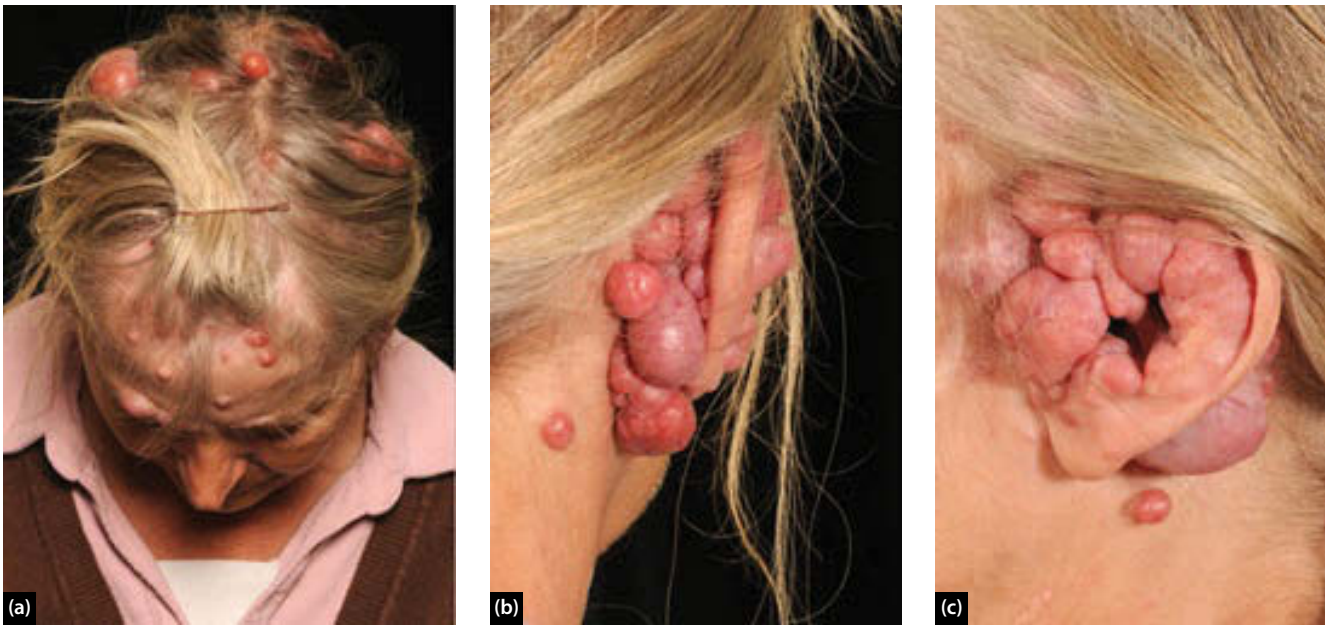
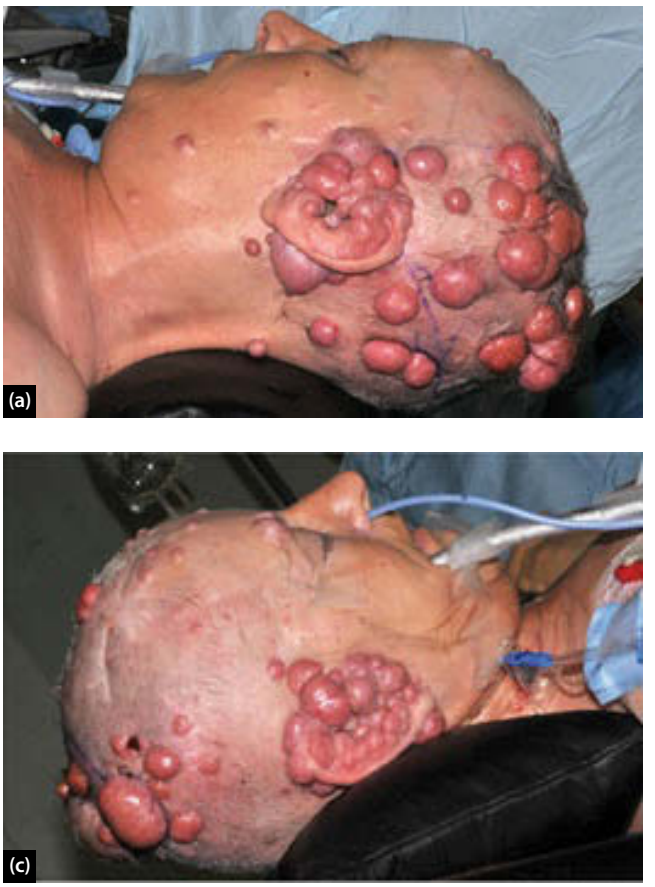


Figure 97.3 Case study 1. The presented cylindroma growth to the scalp and ears.



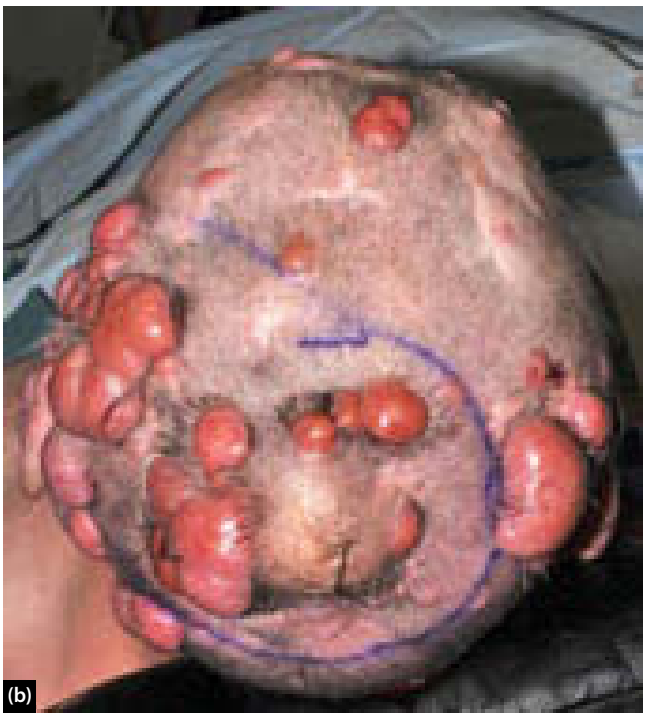


Figure 97.4 Case study 1. The extent of the lesions pre-operatively.

MEDICAL AND SOCIAL HISTORY

She did not smoke or drink and had no other medical complications. Her manual dexterity was adequate, she had family and was very independent.

IMAGING REPORTS

Imaging reports (CT) showed tumours eroding through the vertex of her skull with a lesion of 12 mm × 12 mm attached to the skull. As a result of the complex nature of this case, multidisciplinary input was required.

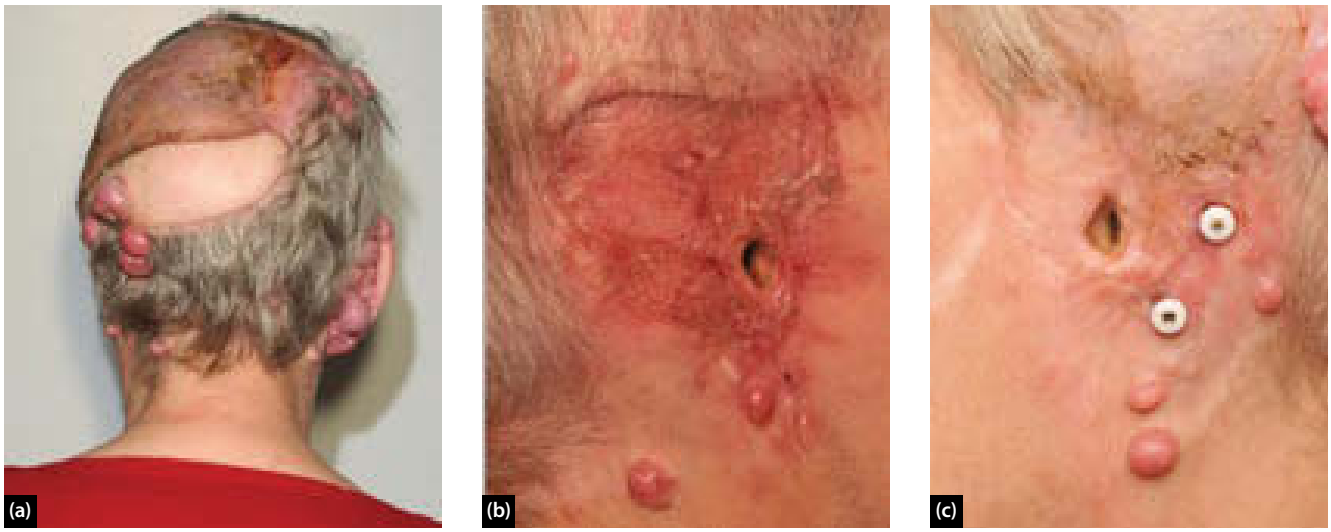


Figure 97.5 Case study 1. (a) Post-operative results of the scalp, **(b)** pinnectomy with first-stage implants and **(c)** second-stage implants with healing caps *in situ*.

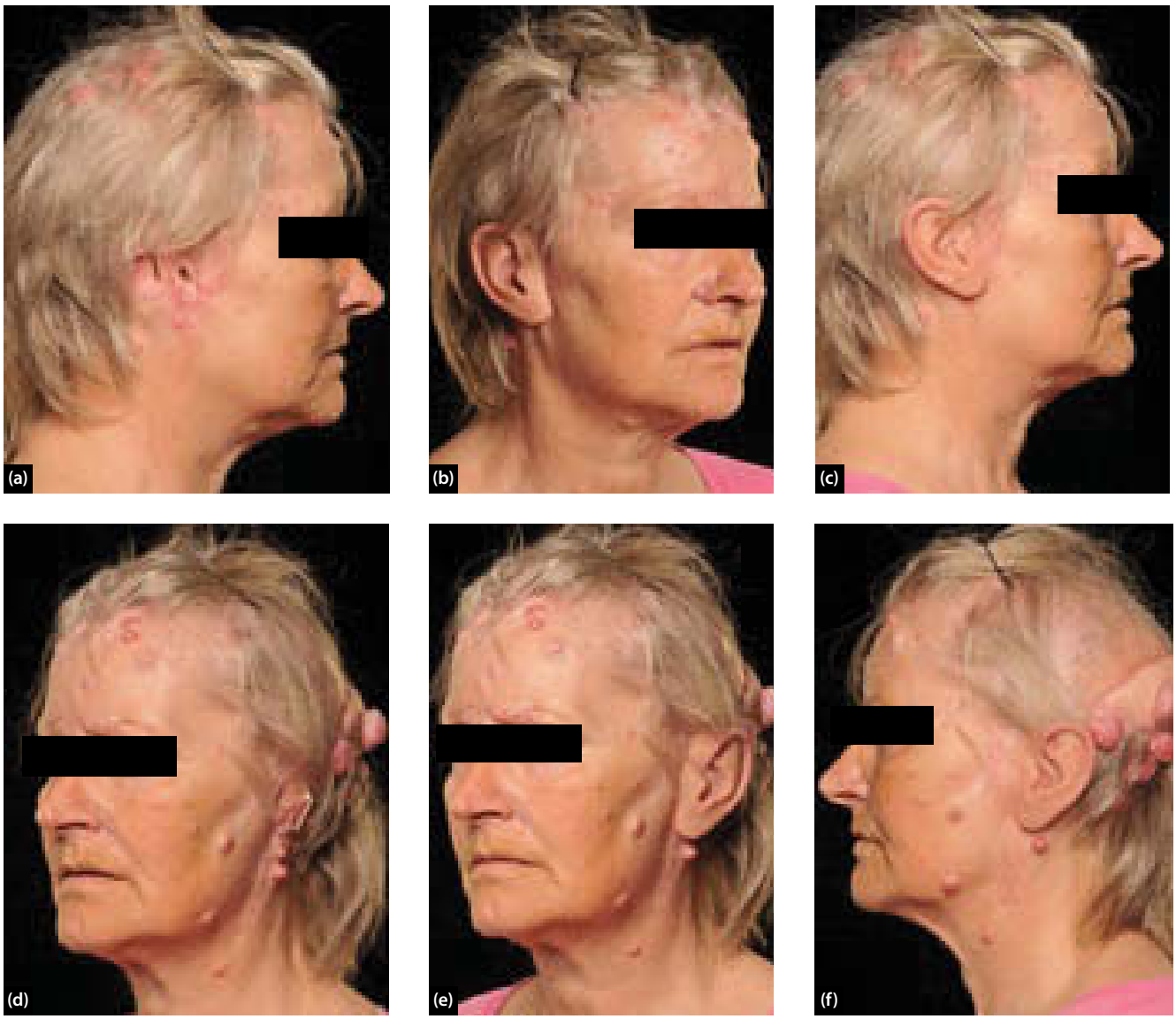


Figure 97.6 Case study 1. (a–c) Final prosthetic results of the right side. **(d–f)** Final result of the left side. Note the implant position varies due to the bone quality at the time of surgery.

Excision of the lesion on the skull and scalp resulted in a substantial defect requiring soft-tissue reconstruction. A free latissimus dorsi flap was used as the multiple cylindromas had precluded the use of her common soft-tissue flap sites and an anterolateral thigh (ALT) flap was too bulky to be used.

The following surgical risks were explained to the patient:

- a 5% risk of flap failure
- deep vein thrombosis (DVT)
- scarring
- infection
- bleeding.

Her ears were virtually destroyed by the coalescing syringomas and required total pinnectomies of both the left and right ears (bilateral), Again, risks were explained.

PATIENT CONCERNS

The patient had aesthetic concerns about the ears and so a prosthetic consultation was required prior to surgery at which the patient and clinician could discuss the treatment options available and consider the best one for her. At this time it was decided that extraoral implants would be inserted at primary surgery as the quality of bone was good, allowing the final prosthesis to be retained using gold bar and clip. It is important the patient has a full understanding of what is achievable and a realistic time frame from start to finish. As the patient's ears were too distorted in this case, a pre-operative impression was not possible.

With further surgical discussions with the surgeon it was decided that the external auditory meatus was to be left intact. As we know, the implant positioning for prosthetic treatment is vital and so the meatus was used to determine the 'ideal' implant placement.

SURGERY

In 2011 the patient had surgical intervention for the lesions on her scalp (**Figure 97.4**) and a staged pinnectomy of the left ear. The ear was removed and two 4 mm implants (first stage) were inserted into the bone. Early in 2012 a pinnectomy on the right side was performed and two 4 mm implants were inserted on that side.

Once the patient had healed, the second stage of the implants was performed. Here a small 4 mm biopsy punch was used to expose the first-stage implants and a healing abutment was placed. This allowed the prosthetist to assess the skin thickness and replace the healing abutment with definitive abutments. On both the left and right sides a 7 mm abutment was used for the upper implant and a 5.5 mm abutment for the lower implant.

PROSTHETIC RESULT

The patient's prosthetic treatment started in August 2012 and the final prostheses were fitted in October 2012 (**Figure 97.6**).

Case study 2

PRESENTATION

A 75-year-old male presented with local crusting to the left alar in 2008 (**Figure 97.7a**).

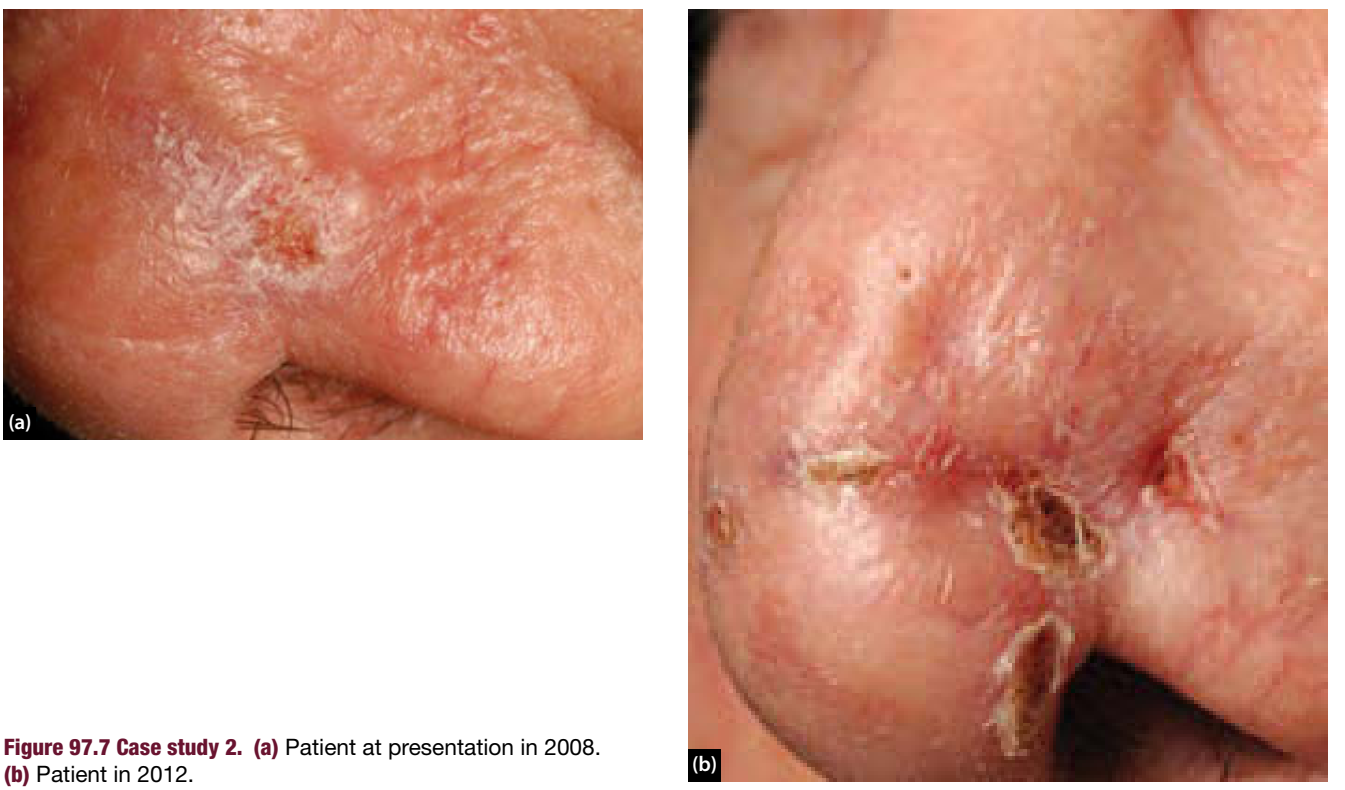


Figure 97.7 Case study 2. (a) Patient at presentation in 2008. **(b)** Patient in 2012.

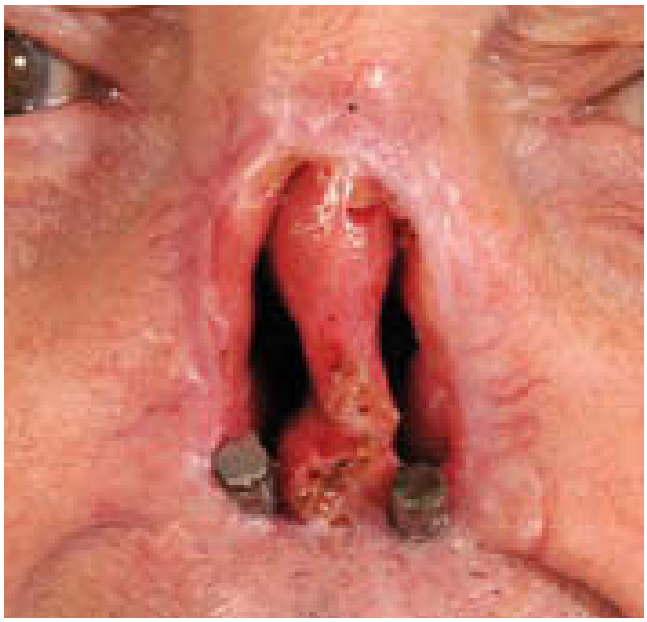


Figure 97.8 Case study 2. Implants fully integrated with a 10 mm abutment on the left and 7 mm abutment on the right. Both abutments can be seen with multiunit magnacaps attached.

MEDICAL AND SOCIAL HISTORY

The patient was a regular smoker who consumed alcohol in excessive amounts on a daily basis. He also had an abnormal growth in the left lung.

DIAGNOSIS

Recurrent squamous cell carcinoma (SCC) involving the entire dorsum and the tip of the nose was diagnosed.

TREATMENT

Although surgical intervention was discussed and achievable with a combination of flaps, the outcome would be inferior to that of prosthetics treatment. It was concluded that the best possible treatment for this patient was to have a total rhinectomy (total removal of the nose) with the insertion of osseointegrated implants followed with prosthetic rehabilitation.

SURGERY

During the procedure two 7 mm Brånemark (intraoral) implants were inserted in the piriform aperture. The reason

Figure 97.9 Case study 2. (a–c) Final result from prosthetic rehabilitation. Profile left, front and right side respectively. **(d)** The prosthesis allows the patient to wear his glasses, which can be advantageous to help hide the edges of a prosthesis.

was dependent on the bone and space available, ensuring there was no interference with the roots of the teeth. In almost all cases, conventional implants such as those used for intraoral reconstruction are suitable. There are clear advantages to using longer implants in terms of long-term survival and load-carrying ability.

Following his surgery the patient was looked after by a clinical nurse specialist who managed his dressing and helped his healing while the implants integrated. Four months after his surgery, in October 2012, the healing abutments were removed and definitive abutments replaced. The height of the abutments should allow clearance from the cavity wall yet allow space for the magnacaps to be attached to the definitive abutments (**Figure 97.8**).

An impression of the defect was taken, recording the accurate positions of the implants using impression magnets. A nasal profile was waxed up using pictures of the patient before he had the rhinectomy. This was then tried and modified according to the patient's requirements. A colour match of the patient's skin was also taken.

PROSTHETIC RESULT

Figure 97.9 shows the final result from prosthetic rehabilitation.

Case study 3

HISTORY

A 64-year-old female had an ongoing symptom of drooping to the right eye. Her optician recorded further drooping to the right eye 3 years after the initial observation. Aged 67 she also had a neuroendocrine tumour in the pancreas, which was picked up after she developed jaundice. As a result, she had a biliary stent inserted early in 2012.

IMAGING REPORT

MRI demonstrated a growth behind the eye, which was excised as a benign tumour in 2012. The biopsy report identified the growth as a lipoma with atypical feature. Following the excision, the patient developed slow progressive proptosis.

DIAGNOSIS

In October 2012 the patient had a further decrease in her vision and developed diplopia. She had another MRI scan, which showed tumour growth above the eye, and a CT scan was carried out to determine bone involvement. A biopsy of the mass showed a myxoid liposarcoma. After further investigations and further discussion it was

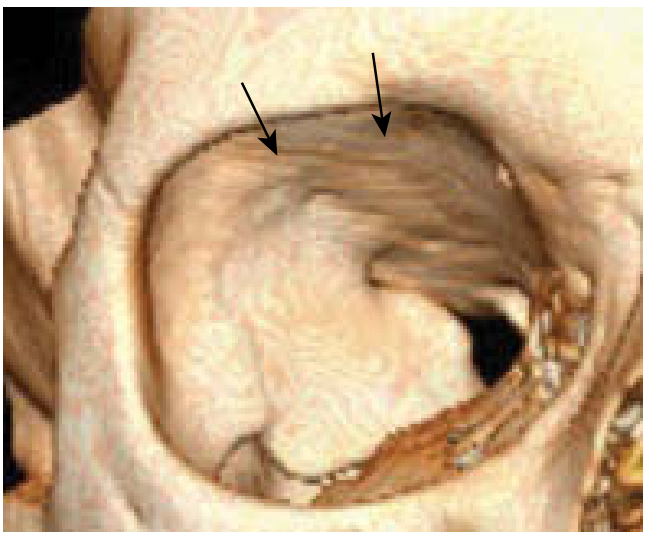


Figure 97.10 Case study 3. Location of the implants.

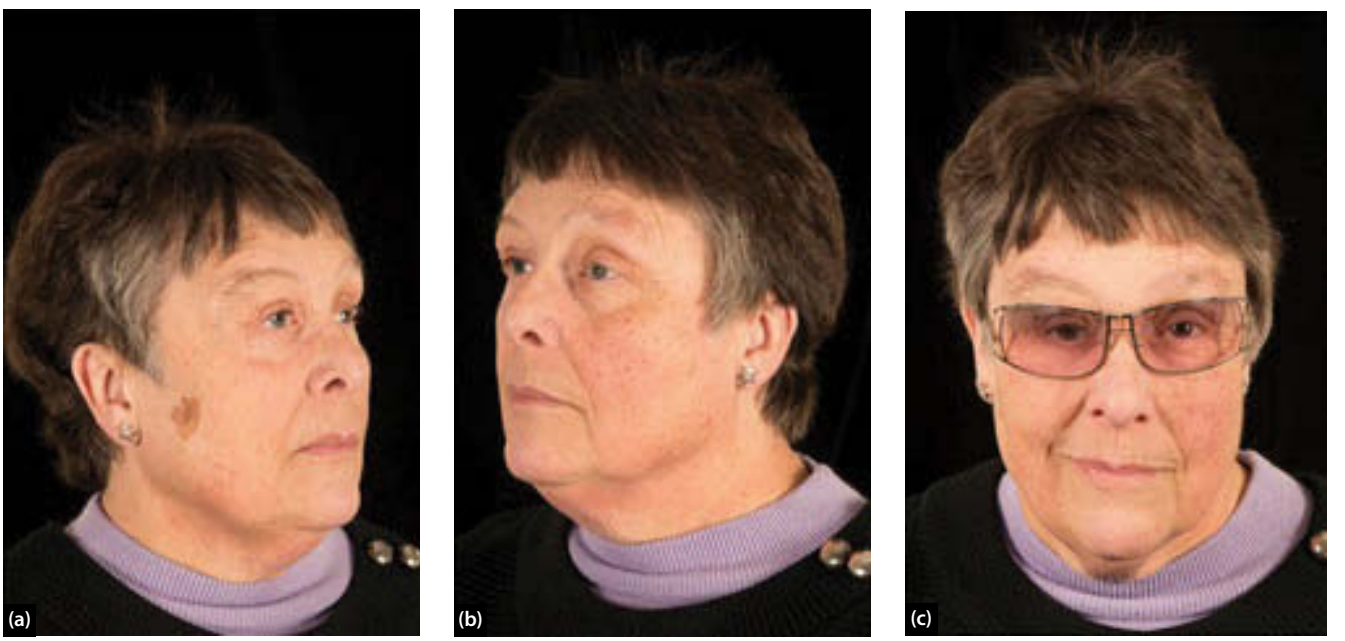


Figure 97.11 Case study 3. (a,b) The right-sided prosthesis *in situ*. **(c)** The use of glasses helps to draw attention away from the prosthesis.

decided that the best treatment was an orbital exenteration with orbital implants followed by prosthetics.

TREATMENT

In April 2013 the patient had the orbital exenteration and two 7 mm dental implants were inserted into the roof of the orbit and left to integrate.

The second stage of the implants was performed at 2 months post-operatively by placing a 2 mm and a 5 mm abutment to the existing implants.

OUTCOME

The final result is shown in **Figure 97.11**.

FUTURE RESEARCH

- There have been many developments in materials used for the production of prosthesis.
- The advent of percutaneous osseointegrated implants has dramatically improved the potential for retention of prosthesis. However, many of the construction methods and mould making have changed little and are highly skilled and time-consuming. Each prosthesis is individual and the use of high technology has been difficult to adapt or is not cost-effective in some individual cases.
- With advances in computer software using CT data, there are programs available that allow 3D simulation of facial reconstructive methods including osteotomy and distraction procedures. Data from medical scanners (CT, MRI) can be used to reproduce physical models of human anatomy via additive layer manufacture (ALM).
- Several ALM techniques exist, the most common is stereolithography. The basic principle of creating a 3D structure is by building layers using the CT data and an optical scanning system that draws a shape one layer at a time onto the surface of the liquid photosensitive resin until the desired model is completed.
- Over the last few years improvements in surgical techniques with the involvement of in-house surgical guide design and enhanced surgical simulation and planning have enabled more accurate and aesthetic reconstructions to be performed. While prosthetic materials continue to be improved and refined, these surgical improvements may render prosthesis to be necessary in a more limited format. The necessity of treating tumours by ablative surgery in the future may be reduced by other treatment regimes and therefore the necessity to surgically or prosthetically reconstruct these defects could be reduced.
- As 3D printing has evolved to build bony structures we still endeavour to find materials and technology to print in silicone materials with the ability to reproduce patient skin texture and colour which may enhance the prosthetic outcome with a view to giving patients a more realistic understanding of the outcome.

KEY POINTS

- Assess patient psychological status.
- Understand patient expectations.
- Build relationships/rapport with patients.
- Keep prosthesis simple for patients to cope with.
- Understand the reconstruction pathway and patient support.
- Understand the importance of facial aesthetic.

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